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A REVIEW OF THE LITERATURE ON INFLUENZA AND THE COMMON COLD

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Introduction.

In connection with the research studies of the United States Public Health Service as to the epidemiology and interepidemic phases of influenza, together with the relation which influenza might bear to the "common cold" and other minor respiratory disorders, the medical literature dealing with these subjects has been reviewed. The matter thus collected seems of sufficient interest to students of the subject to merit publication.

The fact that there is so much in medical literature dealing with this subject indicates that, as yet, our knowledge regarding influenza and the "common cold" is, indeed, very imperfect. Although epidemic after epidemic has swept countries all over the world with almost periodic regularity since the first authentic record (1173), from that time to this there has been lack of agreement among observers as to the etiology and epidemiology of influenza.

In groping for the light on this subject, it would seem that present-day investigators have made little progress over their colleagues of a more remote period. There is even lack of agreement concerning the origin of the name. Dr. A. J. Craft,[1] of Chicago, states:

> The designation "influenza," which means influence, was adopted by the Italians in naming a disease occurring in an epidemic during the year 1743, and since that time many epidemics have been placed under the ban of the influence.

On the other hand, Ditmar,[2] while admitting that the word "influenza" is undoubtedly of Italian origin, states that it was first used in the epidemic of 1742–43 in England, Prindle and Huxham having been the originators of the name. Biermer[3] says:

> We wish to call attention to the fact that "influenza" in Italian does not only mean flux, but also something fluid, temporary, the fashion, and, therefore, also a temporary pestilence, a disease of fashion * * *. In France the influenza has generally been called "la grippe" since the epidemic of 1743. This designation is probably derived from agripper (to attack), and not from the Polish word chrypka (rancedo), as T. Frank believes.

[1] Craft, A. J.: Am. Jour. of Clin. Med., 1919, Vol. XXVI, p. 279.
[2] Ditmar, Finkler: Twentieth century practice of medicine, Vol. XV.
[3] Biermer, A.: Influenza. Virchow's Handbuch der speciellen Pathologie und Therapie, V.

In this connection, Hirsch[4] quotes an observer by the name of Grant, as follows:

"This disease," says Grant in his account of the influenza epidemic of the year 1782, "is prevailing in certain districts of France at the moment of my present writing. It is there called 'la grippe' from an insect of that name, which was very common in England and France during the past spring, and was supposed to have infected the air and imparted an injurious property to it. We know, however, that this view rests upon an error."

The first reference in medical literature to a disease which might be influenza is in the writings of Hippocrates of the period 400 B. C. M. Littre remarks that in the course of his reading he has never found a description of an epidemic exactly like that described by Hippocrates. To quote from Hippocrates:[5]

It broke out in winter about the solstice, and was preceded by great changes of the winds. There was a great tendency to relapses, and it was further complicated with pulmonic affections, nyctalopia, angina, paralysis, etc. It was observed that any member which was much exposed to fatigue was the part most liable to be atacked. All these complications occurred in the relapse, and never in the original attack. Women were less liable to be affected than men, the reason of which is supposed to have been that they do not expose themselves so much to the air as men do. In women, too, all the attacks were mild; but in the men some were mild and others fatal. When a febrile rigor supervened, the attack speedily was mortal. The usual remedies were tried, namely, purging, venesection, bleeding by the renal vein, and emetics; but none of them did any good.

Early Outbreaks and Early Etiological Theories.

METEOROLOGICAL CAUSES.

Hippocrates notes that this epidemic was preceded by changes of the winds. This reference is in keeping with the general observations of this great physician that the direction of the winds and the seasons had a distinct bearing on the epidemicity of diseases, as seen in his aphorisms as follows: "If the summer be dry and northerly and the autumn rainy and southerly, headaches occur in winter, with coughs, hoarseness, coryzæ, and in some cases consumptions"; and, "But if the autumn be northerly and dry, it agrees well with persons of a humid temperament and with women; but others will be subject to dry ophthalmies, acute fevers, coryzæ, and in some cases melancholy."

From that time until 1173 there is little in literature regarding influenza and the minor respiratory diseases. Although an epidemic occurring in that year is mentioned by Hirsch as having affected localities in Italy, Germany, and England, the site of origin and direction and rapidity of spread are unknown.

[4] Hirsch, August: Handbook of geographical and historical pathology, I.
[5] Hippocrates: The genuine works of Hippocrates, translated by Francis Adams.

W. T. Vaughan tabulates 12 epidemics from 1173 to 1510, but it was not until 1510 that the first authentic description of an influenza epidemic was given. This epidemic involved Malta, Sicily, Spain and Portugal, Italy, France, Hungary, Germany, Holland, England, and Norway. It is probable that its origin was at Malta, although this has been questioned, and that it spread generally from south to north.

The publications of Noah Webster[6] in 1799 are interesting as reflecting the popular beliefs of that time, although Webster himself was not a physician. His general indictment of natural influences causing a pestilential state of the air, hence producing epidemics, is apparent throughout his writings. The following quotations from Webster are illustrative of this fact:

The epidemic catarrh is the disorder which most decisively proves a rapid and universal change in the essential properties of the atmosphere. This disease sometimes invades the human race so suddenly that half the inhabitants of a town or city are seized in a night. I do not find the same fact related of any other disease, except the sweating plague in 1529, whose progress through Europe was as rapid nearly as that of the catarrh, and utterly precludes the supposition that infection from fomes had any share in its propagation. * * * From these facts it is evident that the disease is occasioned by an alteration in the atmosphere, but it is observable that whenever it appears on the American Continent it appears also in the islands of the West Indies.

The remote cause usually assigned for catarrh is a sudden change of weather from heat to cold or from cold to heat; the proximate cause, an increased afflux of fluids to the mucous membrane of the nose, fauces, and bronchiæ, with some degree of inflammation. Some medical writers seem to think the remote cause to be the application of cold only to the human body, checking the perspiration by the skin and turning the fluids upon the mucous membrane. * * * The proximate causes of the disease are the province of medical men, but to the influence of the remote cause above stated physicians will pardon me for stating a few objections.

1. The application of cold to the body can not be the sole cause of catarrh, because it appears, and usually with most severity, in the spring, on the abstraction of cold. It is observable also that in many instances its principal violence and mortality are after the return of warm weather, the disease augmenting in violence with the increase of heat. Thus the catarrh of 1709 appeared in Italy, says Lancifius, in January, in severe cold weather, but increased in violence as the spring advanced and the weather moderated.

The same fact took place in the catarrh of 1762 at Edinburgh, where it began in April and increased in violence till June. In the same manner the catarrh in this country, in 1790, appearing in March and April, on the moderation of cold, was far more severe than that of the preceding autumn, when the weather was changing from heat to cold. At least this was the fact in many of the Northern States.

2. It is not always true that the epidemic catarrh appears in spring or autumn, or after great changes of weather. The noted catarrh of 1580 began to appear in Sicily in the month of June; at Rome in July; at Venice and Con-

[6] Webster, Noah: History of epidemic and pestilential diseases, Vol. II.

stantinople in August—in the midst of summer. It is against all probability that this difference can be ascribed to the application of cold. On the other hand, its progress was evidently steady and uninterrupted by either heat or cold. A careful attention to the history of this epidemic at other times will doubtless furnish other similar facts.

The catarrh of 1688 seized Germany in summer; that of 1557 appeared in Spain in August; that in America in 1655 began about the close of June.

3. The appearance of catarrh in tropical climates, as in the West Indies, at the same time it appears on northern latitudes is a strong argument against ascribing it to the application of cold. In the West Indies there is no change of any great consequence in the temperature of the weather; nothing like cold is known in those regions. Yet catarrh, if credible accounts are to be admitted as evidence, is as fatal at times within the Tropics as in any other climate.

It is true that in autumn winds called "norths," or northerly breezes, are experienced in the islands, and these produce colds and coughs similar to what we all experience in temperate latitudes on the change of weather in spring and autumn. But these are very different, at least in degree, from a general epidemic influenza, which seizes mankind in all climate with pain in the side and bones, accompanied often with fever. The universality of this disease, bursting suddenly upon all climates, and raging with equal violence in all seasons, and in defiance of heat or cold, leaves us no room to question its dependence on some other cause than changes of weather or application of cold.

If the application of cold was the sole cause of this epidemic, it would appear at the same time in all places which experience a sudden change from heat to cold at the same time. And, further, a necessary consequence would be it would be epidemic on every such change. Neither of these cases occurs. On the other hand, the disease begins indifferently in any climate and in any season of the year and spreads speedily over whole countries without the least obstruction from heat or cold. And, as far as I can observe from the accounts of it before me, it is as mortal when invading people in hot climates as in cold or temperate regions and seasons. * * * *

It appears to me also that, with deference to the faculty, a strong argument against deriving the disease from sudden changes of weather only may be drawn from a difference in the symptoms of an epidemic influenza and of sporadic cases of the disease obviously contracted by cold. Let me ask practitioners whether in the epidemic catarrh there do not appear symptoms altogether unknown in sporadic cases? But as this is a point that regards practice, it is not proper for me to discuss it.

The celebrated Boyle very justly observes that sudden epidemic colds are not to be accounted for by changes of weather. * * * I do not, however, deny the influence of heat and cold in the epidemic catarrh. In some violent epidemics of this sort heat and cold seem to have little influence, the disease appearing to rage independent of all the sensible qualities of the air. Yet in ordinary cases the temperature of the air seems to *modify*, but not to *generate* or *destroy* the epidemic. * * *

But comets do most evidently occasion at times excessive drouth, and at other times extraordinary quantities of rain, and these intemperate seasons not infrequently succeed each other within a few months. No man can question this fact who attends to the preceding history. All such unusual seasons are apt to injure the vegetable kingdom. In too dry seasons, corn may be defective in quantity; in too wet weather, it is deficient in nourishing qualities; and in both cases, it may contain the germs of epidemic diseases. * * *

Now, it is a fact that will appear from an inspection of the preceding history that, during the approximation of comets to our system, earthquakes have been most numerous, general, and violent. A great proportion of the tremendous eruptions of volcanoes have happened during the same periods. To prove this we need not go back to the terrible concussions and violent discharge of Ætna, which closed the long pestilence in Athens, in the fifth and sixth year of the Pelopponesian war, nor to the dreadful earthquakes and eruption which preceded the destructive plague in the reign of Titus. We have similar facts in modern times. The plagues in the Levant in 1743, and especially in Messina, were accompanied or preceded by violent earthquakes and a comet. The extensive plague of 1760 was attended with all the great phenomena—comets, eruption of Vesuvius, and tremendous earthquakes. The pestilential periods of 1770 and 1783 were introduced by the same phenomena.

These facts afford strong evidence that the approach of comets not only influences the weather, but also calls into action the subterranean fires. By what means those erratic bodies produce this effect may be a curious question. That the internal fires explode at times without the attractive powers of comets is undoubted; but the concurrence of earthquakes and violent discharges from volcanoes during the presence of comets, or near the time, seems to render it certain that those bodies have a most powerful effect on the element of fire which is diffused through the globe and the surrounding atmosphere.

Many authors have observed this connection between comets, earthquakes, and pestilence, but seem not to have included volcanic eruptions among the causes of disease.

Webster also presents a table of influenza epidemics in the world since 1174, with notes after each year calling attention to comets and volcanic eruptions. Some of these are as follows:

Catarrh epidemic in—

1174, the year *before* an eruption of Etna, and followed by great mortality. (Chasm in the accounts of this disease.)

1510, the *same* year with an eruption in Iceland, and following great earthquakes. Humid air—a comet appeared the next year. (Chasm.)

1551, the year *after* an eruption of Etna, and a comet. Season wet.

1557, the year *after* an eruption of Etna. Season mostly wet; but in some countries dry; a comet the same year. (Chasm.)

1580, the year *after* an eruption of Etna. Cool, dry north wind, a comet.

1587, the *same* year with an eruption in Iceland, and *after* a comet.

1591, *after* earthquakes in 1590, and a comet.

1597, the year *after* earthquakes and a hard winter; rainy season and a comet the same year.

1602, the year *after* earthquakes, volcano, and severe winter. Cold and wet season.

In like manner he describes 35 more epidemics.

SPECIFIC CONTAGION.

In 1803 Richard Pearson,[7] of London, took issue with the observers who thought that the weather had any influence on the

[7] Pearson, Richard: Some observations on the present catarrhal fever or influenza, chiefly in relation to its mode of treatment. To which are subjoined historical abstracts concerning the catarrhal fever of 1762, 1775, and 1782. 8° London, 1803.

spread of colds and influenza, leaning instead to a belief in the spread of influenza by personal contact. He says:

A variable state of the weather has been supposed by some to be the exciting cause; but if this were the case, catarrhal fevers or influenzas should appear epidemically every winter or spring, for in this climate, at least, the weather is notoriously changeable at those seasons of the year. But there is one circumstance which puts it beyond a doubt that sudden alterations of heat and cold, wet and dry, are not the cause of this disorder (although they may modify and favor the action of other epidemics); I mean its existence at a time of the year when such variations of the atmosphere do not take place. The influenza of 1782 was prevalent in many parts of England and in the months of June and July, when the weather was such as is usual in our finest summers; and one of the most remarkable epidemics of this sort made its appearance in Germany and other parts of the continent of Europe in the autumn of 1580. With more appearance of probability has the origin of this epidemic been referred to specific miasmata diffused through the lower regions of the atmosphere. It is difficult, however, to conceive how the air should become impregnated with these miasmata in such quantity as to render it (the air) capable of exciting the disease over a tract of the globe containing many thousand square miles (for to such extent did the catarrhal fever of 1782 prevail); and why, if an atmospherical agency of this sort were the only cause, the disorder should not show itself in all places within the distance of a few hundred miles at one and the same time, and not progressively at different periods. But though it should be granted that the disease originates from miasmata existing in the lower currents of the atmosphere, it by no means follows that it is not kept up and rendered epidemic by personal intercourse; i. e., by effluvia emitted from the bodies of the sick, particularly by the breath. Intermittents, the offspring of marsh miasmata, are sometimes transferred from their native swamps and rendered epidemic even in dry and elevated situations, by the same means, viz, by contagion. If, in populous towns and in houses consisting of large families, numbers of persons are seized with influenza nearly about the same time, it does not necessarily mean that it is propagated by the atmosphere alone and not by individual communication, or infection as well or chiefly. For among the numbers which fall ill in different parts of the town many must have had intercourse with others who were actually suffering under the disorder or recovering from it; and where several persons under the same roof are seized on the same day, it is certainly proof that they did not infect one another, but may rather be assumed as an argument of the very active and diffusible nature of this specific contagion.

One of the earliest discussions of the possible seriousness of what are called "colds" was made by Dr. Thomas Hayes[8] in his book which was published in Dublin in 1789. This observer considered only exposure as a cause, but he does emphasize the dangers of allowing colds to go unguarded. He says:

A cold arises from the effect of cold or moist air applied to the surface of the body and lungs from going too thinly clad or exposing the body to cold air after having been heated by exercise, or when the pores are opened from drinking warm liquors, etc.

[8] Hayes, Thomas: A serious address on the dangerous consequences of neglecting common coughs and colds, with directions devoted to the prevention and cure of consumption, to which are now added observations on whooping cough and asthma. 4th ed., Dublin, 1789.

A cold, then, is a sense of chilliness on the skin attended with a lassitude or weariness and slight shivers at times, with a degree of headache and flying pains in the small of the back and limbs, a stuffing of the nose, frequent sneezing, and running of a clear, limpid water from the eyes and nose, with or without a dry, tickling cough or hoarseness. Sometimes the sneezing, stuffing of the nose, or cough gives the first intelligence of its approach, and sometimes it is preceded by some of the other symptoms. These, as they are found to come on with more or less violence, permit the patient to continue in the usual employment or pleasures until they get so far increased or have laid such hold on his constitution as to oblige him to desist, unless nature by some happy effort restores the obstructed vessels to their proper offices and causes the several fluids to be circulated through the proper tubes. If the patient is not relieved in this way, fever, rheumatism, inflammation of the lungs, or some other disease must ensue.

Nothing perhaps contributes more to strengthening the constitution and renders the body less liable to catch cold than bathing in the cold bath or in the sea. * * * The advantages derived from washing children in cold water every morning can not be too often enforced on the attention of parents. It strengthens their tender limbs and keeps them from the ricketts and the habit of taking cold. Children can not be to soon inured to bear all kinds of weather.

Other factors given by Hayes as the cause of colds are:

Sitting in rooms after they have been just washed;
Letting wet clothes dry upon the back;
Sitting in cold, damp churches;
Sitting in cold rooms;
Beds not having been lain in some time contract a damp particularly hurtful to many; and
Ill-dried linen.

Quite different from the beliefs that winds, volcanoes, and comets were the causes of influenza, yet apparently indicating that epidemics may be caused by unusual natural disturbances, are the observances of Rollo Russell, who made the following contribution as to his idea of the causation of the epidemic of 1888, in the Twentieth Century Practice of Medicine. He stated that—

Great inundations occurred in China in 1888 by the overflowing of the Yellow River. It is said that 1,700,000 persons were drowned at this time, and immense regions were undoubtedly inundated. Six months later similar enormous floods occurred in Manchuria. As a result of this calamity this locality was visited by a great famine in the summer of 1889; cholera also appeared; and during the winter another plague caused great perturbation among the inhabitants. During the summer the flooded portions dried up and were covered with the yellow dust which had been deposited as slime by the Hoang Ho. The dry winds now drove the dust in such quantities into the air that the sun was obscured. Thus it would seem probable that the innumerable organic germs from the Yellow River might have been carried over a great extent of country.

Modern Etiological Opinions.

It was not until after the epidemic of 1888 had swept the world that Pfeiffer, in 1890, isolated a small Gram-negative bacillus in

great numbers from smears in cases of influenza. These findings were confirmed by Yanagisawa,[9] who says in his conclusions:

1. *B. influenzæ* shows some symbiotic reaction with *Dipl. pneumoniæ*, *Dipl. catarrhalis*, staphylococcus, and streptococcus. It promotes the toxic action of any of the latter. Especially that of *Dipl. pneumoniæ*, *Dipl. catarrhalis*, and, inversely, its own toxic action (of these cocci) is also promoted in this symbiotic relation.

2. The increase of the toxic action of *B. influenzæ* is, however, by far the smaller in comparison with the promotion of the toxic action of these cocci caused by *B. influenzæ*.

3. In the symbiotic experiment with *B. influenzæ* mixed with *Dipl. pneumoniæ* and streptococcus, it is very difficult to isolate *B. influenzæ* from the cardiac blood of dead mice. Only in two cases in which streptococci were used for symbiotic microbes was *B. influenzæ* cultivated.

4. From the above facts it may very reasonably be supposed that, in a pandemic of influenza, *B. influenzæ* first enters into the respiratory system and then develops the typical symptoms of the disease, provided that none of the above-mentioned cocci are present. In that case *B. influenzæ* can be cultured purely from the secretions of the patients. If, on the other hand, *B. influenzæ* enters into a symbiotic relation with any of the above-named cocci, it intensifies the toxic action of the latter, and strong secondary symptoms will be the result. In that case the propagation of *B. influenzæ* would be overlapped by that of the cocci. This is the possible reason why we were able to isolate these cocci in a larger number of cases than those of *B. influenzæ*. The fact, therefore, that only cocci were isolated from the pneumonia tissues of dead objects is no direct proof for the assumption that there was no primary infection of *B. influenzæ*.

Martin Kristensen, after an investigation into the occurrence and classification of the hæmoglobinophilic bacteria, says:

From my own experience and that of others it is maintained that in all probability Pfeiffer's bacillus is not to be looked upon as the primary specific virus of influenza.

Cecil and Steffen,[10] in the Journal of Infectious Diseases, give the following conclusions:

Virulent influenza bacilli, when injected into the nose and throat of healthy volunteers, may excite in them an acute respiratory disease, similar in many respects to influenza, but falling short of the typical clinical picture.

In such cases influenza bacilli, biologically identical with those inoculated, may be recovered from the discharges as long as symptoms persist and often for some time thereafter.

Filtrates of *B. influenzæ* cultures, when similarly injected into two healthy volunteers, produced neither local nor constitutional reaction.

The inoculation of healthy volunteers with virulent hemolytic streptococci may in some cases induce an acute follicular tonsillitis with fever and leukocytosis. A virulent pneumococcus type 4, on the other hand, was injected into the nose and throat of two healthy volunteers with impunity.

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[9] Yanagisawa, S.: Experimental study of the mixed infection of *Bacillus influenzae* and various species of cocci. Kitasato Archives of Internal Medicine, 1919, Vol. III.

[10] Cecil, Russell L., and Steffen, Gustav I.: Acute respiratory infection in man following inoculation with virulent *Bacillus influenzæ*. Jour. Inf. Dis., 1921, Vol. XXVIII.

Since that time other organisms have been isolated, advanced, and given a certain amount of publicity, with the result that all of them have been more or less discarded.

In 1914 active work was begun to show what rôle, if any, the filtrable viruses played in the etiology of common colds and influenza. One of the first observers along these lines was Dr. E. Kruse,[11] who pointed out that while common colds are undoubtedly infectious, the paucity of bacteria in the secretions and the short time that these few persist militate against the presumptive evidence that they are concerned in the infection. Kruse produced colds experimentally with filtered nasal secretions, and claims to have demonstrated living organisms in his filtrates by bacteriologic methods, concluding that the causative organism should be classed with the filtrable viruses.

In 1917, Maj. George B. Foster,[12] of the United States Army, from his experiments, concluded that common colds are infectious, being due to a filtrable virus, and that it was possible to transmit colds to man experimentally. His description of his work follows:

> As a rule, the plates prepared from secretions collected within 24 hours of the onset, while the nasal secretion was thin and clear, remained sterile or showed, at most, but few colonies, the identity of which varied in different cases. Many writers note this paucity of bacteria in the nasal secretions from early coryzas. On the other hand, secretions that had become mucopurulent or blood-streaked uniformly gave innumerable colonies in plate cultures, but here, again, there was no uniformity in the findings. I desire to lay emphasis on the negative findings in early cases as challenging the popular belief that the nasal cavities furnish a normal habitat for various bacteria capable of pathogenicity under certain conditions. Numerous workers have shown that the normal nasal mucosa is sterile or practically so. Cecil, in an investigation of *Streptococcus viridans* in its relation to infections of the upper respiratory tract, found that cultures from coryzas in the acute stage were often sterile, and he states that cultures taken in the subacute or chronic stages often show so many different types that it is difficult to decide which organism is the causative factor. He further found that *Streptococcus viridans* infections nearly always start in the throat and extend upward and downward or both.

After inoculation experiments with filtered discharges for the first three days' duration, he makes the following observations:

> Analysis of the results of these experiments showed that of the 10 men inoculated, 7 developed clear-cut and definite symptoms of acute coryza, 2 reacted questionably, while 1 remaining case exhibited no symptoms. The results of the inoculation experiments with nasal secretion filtrates and the sterility of these filtrates as regards microorganisms capable of demonstration by ordinary bacteriologic methods seemed to indicate clearly that the infective agent is a filtrable virus.

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[11] Kruse, E.: Die Erreger Von Husten und Schnupfen. Munchen Med. Wchnschr. 1914, LXI, p. 1547.

[12] Foster, George B.: Etiology of common colds. Jour. of Inf. Dis., 1917, Vol. XXI, p. 451.

Major Foster's conclusions are as follows:

1. Common colds of the ordinary type are infectious.

2. The ordinary bacteriologic methods that have been resorted to heretofore do not furnish reliable criteria on which to base conclusions as to the etiology of these infections. Cultures made from the nasal secretions early in the acute stage often remain sterile, while cultures made later in the attack frequently show such a diversity of organisms that only presumptive evidence exists for ascribing to any one an etiologic rôle.

3. It has been demonstrated experimentally that the virus of common colds occurs in the nasal secretions, and that this virus is capable of passing through Berkefeld filters which are impermeable to ordinary bacteria.

4. By the employment of special anaerobic methods the virus of common colds has been cultivated in vitro and has proved capable of repeated recultivation in subcultures.

5. Experimental inoculations have demonstrated that Berkefeld N filtrates of subcultures of the virus, in the second generation at least, are infective.

6. A peculiar minute microorganism has been isolated from cultures made from the filtered nasal secretions in common colds. This microorganism can be passed through Berkefeld N filters and has been recultivated from culture filtrates. Although conclusive proof of its nature has not been adduced, the experiments suggest that the microorganism described bears a definite relation to the true infective agent.

In 1918 Gibson, Bowman, and Connor [13] reported to have obtained a filtrable virus from early cases of influenza and to have transmitted the disease to monkeys. Their conclusions follow:

1. Two rhesus monkeys inoculated subconjunctivally and intranasally with the filtered sputum from cases of human influenza became ill on the sixth and seventh days, respectively—that is, after a period corresponding closely with that noted in human cases under similar conditions by MM. Nicolle and Lebailly.

2. Two control monkeys, kept in the same room under similar conditions, manifested no signs of illness during the same period.

3. Of the two inoculated monkeys, one rapidly regained normal health, all symptoms appearing to have subsided by the third day of the attack. The other seemed to be on the mend on the afternoon of the third day, when it was killed for further examination. In the animal the respiratory tract was found to show the presence of a hemorrhagic exudate affecting especially the lower lobes of both lungs. The condition found was in many respects comparable to that noted in certain human cases of influenza in which a fatal issue had supervened before the occurrence of marked secondary infection. In this connection it is interesting to recall the tendency to hemorrhages which has so often been noted during the present influenza epidemic and which is generally observed early in the disease.

4. Two rhesus monkeys, Nos. 3 and 4, at first used as controls and subsequently inoculated, the one with filtered, the other with unfilterd sputum collected from a case of influenza on the sixth day of the disease, showed no symptoms and remained well.

5. Our observations, so far as they go, tend to confirm those of MM. Nicolle and Lebailly above quoted.

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[13] Gibson, H. Graeme; Bowman, F. B.; and Connor, J. I.: A filtrable virus as the cause of the early stage of the present epidemic of influenza. Brit. Med. Jour. Vol. II, 1918, p. 645.

6. The post-mortem appearances are undoubtedly suggestive, and further work in this direction may throw considerable light on the question.

In 1923 Olitsky and McCartney,[14] of the Rockefeller Foundation, made studies on the nasopharyngeal secretions from patients with common colds. In brief they confirmed the previous work of Kruse and Foster and stated in their report as follows:

The transmission of a clinical condition similar to typical infectious common cold from man to man with the filtered nasopharyngeal washings of early cases of the disease indicates that the incitant is filterable, thus confirming the earlier observations of Kruse and Foster.

Experiments on rabbits with these secretions and cultivation tests show that the materials derived from patients with common colds are distinct in effects from those of epidemic influenza.

Cultivations of the nasopharyngeal washings from 40 cases and from the lung tissue of inoculated rabbits have failed to reveal any constant pathogenic agent or incitant. Although a careful search was made for the "globoid bodies" of Foster in these materials, we have been unable to find them. None of these cultures, furthermore, yielded *Bacterium pneumosintes.*

In its edition of November 17, 1923, page 1697, the Journal of the American Medical Association commented on the work of the etiologic agent in the common colds as follows:

The etiologic agent in the production of the common cold has been singularly elusive. The disease, if it deserves this imposing designation, is a mild one in man. There are few, if any, significant constitutional reactions from it, and consequently it is not easy to ascertain whether the malady has been transmitted in animal experimentation. For this reason, attempts to infect animals with the common cold of man have borne little fruit of the nature of positive achievement. Efforts to transmit the possible incitant directly to human subjects, though few, have been somewhat more promising. The latest of such trials, conducted by Olitsky and McCartney at the Rockefeller Institute for Medical Research, indicate that the incitant is a filtrate agent obtainable from the nasopharyngeal washings of patients during the very early hours of the onset of the symptoms. At least, with such filtrates the symptoms of common cold have been transmitted to a number of healthy persons. Transmission failed in cases in which the "colds" were caused by exposure to the elements, or chilling of the body, and not by definite contact with other cases of common colds. Evidently there are colds and colds; but it will be an unmixed blessing when the cause of any brand of these commonest sources of malaise can be captured, properly indicted and then promptly executed.

In 1920 Schmidt,[15] from a series of 196 filtrate inoculations from 16 different subjects suffering with coryza, concludes that his investigations do not support the filtrable virus theory of "colds."

In 1921 Branham and Hall,[16] from their experiments, concluded that there is no evidence whatever to support the theory that the

[14] Olitsky, Peter K., and McCartney, J. E.: Studies on the nasopharyngeal secretions from patients with common colds. Jour. of Exp. Med., Vol. XXXVIII, No. 4, Oct. 1, 1923.

[15] Deutsch. med. Wchnschr., 1920, 46, p. 1181.

[16] Branham, Sara E., and Hall, Ivan C.: Attempts to cultivate filtrable viruses from cases of influenza and common colds. Jour. Infec. Dis., Vol. XXIII, 1921, p. 142.

cause of common colds and influenza is a filtrable virus. In their own words:

During the winter of 1919–20 we attempted to cultivate filtrable viruses from certain respiratory infections, employing the technique of Foster and, in addition, other methods that seemed promising. Fifty-five samples of nasopharyngeal secretions from 44 individuals have been studied, 38 of the samples being from common colds, 9 from influenza, and 8 from normal persons. Most of the colds were simple acute rhinitis; 7 were accompanied by a bronchitis, 1 by pharyngitis, 2 by sinus tis, 1 by tonsilitis, and 1 proved to be a nasal diphtheria.

These experiments offer no evidence in support of the theory that the cause of either common colds or influenza is a filtrable virus.

In attempting to cultivate filtrable viruses from the nasopharyngeal secretions in colds and influenza no bodies were found in the "cultures" which could not be found also in those from normal persons, in controls, in all simple mediums examined, and on blank slides.

It is recognized that negative experiments, limited to the attempted cultivation of a filtrable virus, and including no attempts to reproduce the disease in animals, do not offer conclusive evidence that such a virus is not involved.

No conclusions can be drawn concerning influenza on account of the few cases examined, together with the fact that samples of such were not collected during the earliest stages of the disease.

However, the uniformly negative results obtained with a large and representative number of colds are not without significance.

Yamanouchi, Sakakami, and Iwashima,[17] in 1919, report that their observations do not support the theory that influenza is a filtrable virus. Their summary is as follows:

1. The germ of influenza can not be removed by filtering (filterable virus).
2. The germs can infect through the mucous membrane and also by inoculation.
3. The germs can be found in the sputum and the blood of influenza patients.
4. The known bacilli, such a Pfeiffer's bacillus, pneumococci, and some diplococci, are not the cause of influenza.
5. We observed experimentally that all people who have previously had influenza or received the sputa emulsion or its filtrate are immune to the disease.

The latest observers to express their opinion in the negative are Robertson and Groves,[18] who reported in April, 1924, the following:

Results of the 100 human inoculations are: Positive for bronchitis, 1 case (1 per cent); coryza, 1 case (1 per cent); influenza, 1 case (1 per cent); laryngitis, 2 cases (2 per cent). There were 95 negative cases (95 per cent) free from any respiratory infection following inoculation.

Twelve days allowed for incubation.

In any group of persons selected at random during a time when an epidemic of colds is present a certain small percentage will develop upper respiratory infection within a period of 12 days. This, we believe, fully explains the cases which we recorded as positive.

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[17] Yamanouchi, T., Sakakami, K., and Iwashima, S.: The infecting agent in influenza. The Lancet, June 7, 1919.

[18] Robertson, R. C. and Groves, R. L.: Experimental human inoculations with filtered nasal secretions from acute coryza. Jour. of Inf. Dis., April, 1924, p. 400.

In this series of experiments nasal secretions were secured from 11 persons suffering with acute uncomplicated coryza. After being diluted and passed through a Berkefield filter these secretions were sprayed onto the nasal mucosa of 100 volunteers.

The experiments presented no convincing evidence indicative of a filter-passing organism as the exciting factor in acute coryza. We believe the cases recorded as positive to be the result of factors independent of the inoculations.

During the attack of coryza definite variations were noted in the bacterial flora of the secretions. During the onset and early stage of the attack there was a marked diminution of the total bacterial flora, with an equally marked predominance of one of the normal habitants, usually *Staphylococcus albus*.

During the purulent stage of the attack a marked increase of all organisms over the normal flora of health was observed, although the predominance of one organism still remained. The later stages of the attack were marked by a gradual return to the normal flora of health.

It can be seen from these few experiments by a limited number of experimenters that opinions are by no means uniform as to whether or not the cause of influenza is a filtrable virus, nor has it been possible to transmit influenza experimentally by inoculating the nose and throat of volunteers with the Pfeiffer bacillus. Experiments[19] carried on jointly in Boston by Doctors Rosenau, Keegan, Goldberger, and Lake and in San Francisco by McCoy and DeWayne Richey have not shown that the Pfeiffer bacillus can be transmitted directly to the nose and throat of volunteers.

Wahl, White, and Lyall[a] succeeded only in getting negative results in their efforts and experiments to transmit influenza bacteriologically by the application of filtrates and suspensions to the nasal mucosa. A part of their conclusions follow:

The nasal application of a filtrate from a pneumonic lung of an individual dead from typical influenza broncho-pneumonia failed to call forth any abnormal symptoms.

The application to the mucous membrane of the nares and nasopharynx of five healthy men (four inoculated from 4–6 weeks ago against influenza with a polyvalent influenza vaccine, one uninoculated) of freshly prepared suspension of four different live strains of *B. influenzæ* (one, in the second generation from the fatally infected human host) even in the massive doses failed to produce any abnormal symptoms.

The implantation of living suspensions of influenza bacilli produced no material alteration besides the addition of the influenza bacillus itself.

The Journal of the American Medical Association in an editorial, November 9, 1918, commenting on abstracts from German and English articles on the epidemic of 1918, admitted that up to that time nothing was known regarding the etiology of influenza. To quote:

[19] Some interesting though unsuccessful attempts to transmit influenza experimentally. Pub. Health Rep., Jan. 10, 1919.

[a] Wahl, H. R., White, George B., and Lyall, H. W.: Some experiments on the transmission of influenza. Jour. Inf. Dis., XXV, 1919, p. 419.

The highly interesting abstract of recent English and German articles on so-called epidemic influenza, prepared by the British Medical Research Committee and printed verbatim in this issue of the Journal, invites a few brief comments. The abstracts do not convey any clear information as to the extent of the spread or the severity of the disease in Europe. Judging, however, from the number and the nature of the articles abstracted, it looks as if the disease, thus far at least, has been more severe and more extensive in Germany than in England. One also receives the impression that the results of the bacteriologic and anatomic studies in Germany correspond more closely, perhaps, to the results that are being obtained in this country than do those coming from England. But it is entirely too early, of course, to form any reliable conclusions.

The articles abstracted seem to have been meager in clinical detail. It is evident that the observations at hand do not indicate the present epidemic to be a distinct clinical entity, clearly differentiated in its clinical activities from similar previous epidemics of more limited extent. The present epidemic apparently differs from these earlier epidemics mainly in contagiousness and in its extensive spread. The many minor epidemics of respiratory infections preceding the present epidemic are of great epidemiologic interest, but their true relation to the European influenzal disturbance can probably not be traced accurately. The fundamental anatomic changes in influenza, according to German reports, seem to have been hemorrhages, especially in the respiratory tract, as well as inflammatory foci, the whole suggesting to some of the investigators a primary infection of the blood with localization especially in the pulmonary vessels. It would seem, however, that the possibility of direct infection of the respiratory tract can not be excluded. These changes are regarded as paving the way for secondary infections. It is of great interest that there is no unanimity of opinion whatever as to the nature of the primary infecting agent.

The bacteriologic results do not appear to warrant the assignment of any greater importance to the influenza bacillus than to the organisms described as diplo-streptococci. These diplo-streptococci are not described fully, but they most probably are nonhemolytic streptococci of the *viridans* type. Only slight mention is made of hemolytic streptococci or of pneumococci, which appear to be isolated in a certain proportion of the cases of influenzal pneumonia in this country.

On the whole, the results of the work covered by the abstracts support the conclusions that we do not understand the true nature of the condition being called epidemic influenza; that there is not sufficient evidence to regard any one of the different forms of bacteria found in the respiratory tract in the cases of the disease as the primary cause, but that all the bacteria, the influenza bacillus as well as the so-called diplo-streptococci and others, may be secondary invaders, transmissible from person to person with almost the same ease as the supposed, but unknown, primary cause. The one experiment mentioned bearing directly on the question of the exact etiology of epidemic influenza is that by Selter, who produced a typical but mild attack in two persons by spraying the throat with a filtrate of influenzal throat secretions, but not enough details are given so that one can form any judgment as to the value of this experiment.

Coincident with attempts to demonstrate, without uniform results, that the etiologic agent of colds is a filtrable virus, other bacteriological studies have been in progress, with efforts to place the respon-

sibility on a definite organism. George Mathers,[20] of Chicago, has suggested a new streptococcus as a possible factor and summarizes his findings thus:

During the winter of 1915–16 an epidemic of acute respiratory infection occurred in Chicago which closely resembled in its clinico-anatomical manifestations and epidemiology so-called true influenza as it appeared in 1889–1892.

In a bacteriological study of material from 61 cases of this disease the influenza bacillus was found in only one instance, and then in small numbers. On the other hand, virulent hemolytic streptococci similar in cultural characteristics and virulence to the streptococcus commonly associated with epidemic sore throat and scarlet fever were found in the nose, throat, and pharynx in 46, and in the blood in 3 cases of this epidemic disease.

Streptococcus viridans and the pneumococcus were each found in 30 instances, these organisms in virulence and biologic characters closely resembling the organisms found in the normal mouth.

The predominance in the discharges from the nose, throat, and pharynx of patients suffering from the epidemic respiratory infection of a virulent hemolytic streptococcus not usually found in the normal mouth, the absence of the influenza bacillus, and the character of the associated pathologic changes suggest that this disease was caused by a virulent hemolytic streptococcus.

Ruth Tunnicliff[21] in 1920 made the following observations:

Various investigators isolated peculiar green-producing cocci with characteristics, both pneumococcus and streptococcus, from influenza and its complications. I have isolated this coccus from the œdematous brain in influenzal broncho-pneumonia, and generally in pure culture. In no instance was the Pfeiffer bacillus cultivated from the brain.

The serum of rabbits immunized with strains of this coccus from influenza and its complications contained opsonins and agglutins for other similar bile-insoluble influenzal cocci and also for certain influenzal cocci which were bile soluble and agglutinable by antipneumococcus serums.

These results indicate that the green-producing influenzal cocci form a group, the members of which are closely related immunologically.

Experiments of great interest and of no little importance are those carried on by Olitsky and Gates[22] of the Rockefeller Foundation, in which *Bacterium pneumosintes* was demonstrated. The authors do not make extravagant claims that it is the sole cause of influenza, suggesting, instead, that it might pave the way for a discovery of the true etiologic factor. To quote their summary:

It would, of course, be a simple matter to announce the inciting or etiological agent of epidemic influenza in man to be the minute, bacilloid organism here described. At present such a course does not seem desirable, even though the clinical and pathological effects induced in the rabbit simulate so closely the phenomena found in epidemic influenza in man. Apparently we are at the threshold of our knowledge of a group or class of minute microorganisms which the anærobic Smith-Noguchi technique has thrown open to exploitation. It

[20] Mathers, George: Bacteriology of acute epidemic respiratory infection commonly called influenza. Jour. of Inf. Dis., Vol. XXI, 1917.

[21] Tunnicliff, Ruth: Observations on green-producing cocci of influenza. Jour. of Inf. Dis., May, 1920, 26: 404.

[22] Olitsky, Peter K., and Gates, Frederick L.: Jour. Inf. Dis., 1921, Vol. XXVIII.

seems wiser, therefore, to defer decision of the precise relation which the species described in this and previous communications bears to epidemic influenza until further experience is obtained.

In the meantime it is desirable to give the microorganism a name, and since a striking feature of its effect in rabbits is to diminish the resistance of the lungs to the action of ordinary pathogenic bacteria, as will be shown in a forthcoming paper, the name of "*Bacterium pneumosintes*" is proposed (from the Greek words meaning lung and devastator).

From the filtered nasopharyngeal washings of patients in the first 36 hours of uncomplicated epidemic influenza and rarely in later stages of the disease, we have cultivated a minute bacilloid body, *Bacterium pneumosintes*, 0.15 to 0.3 micron in length, of constant cultural characters and capable of indefinite propagation on artificial media. This organism, not of the nature of ordinary bacteria, was also recovered in pure culture from the unfiltered and filtered lung tissue of rabbits and guinea pigs inoculated with unfiltered and filtered nasopharyngeal washings of early influenza cases, both from the first epidemic of 1918–19 and from the second one of 1920. The organism grows only under strictly anærobic conditions, passes Berkefeld V and N filters, and withstands the action of sterile 50 per cent glycerol for a period of months.

It has been recovered from cultures contaminated with a variety of ordinary bateria such as *Bacillus pfeifferi*, pneumococci, streptococci, and staphylococci, and has been experimentally cultivated in symbiosis with them.

Similar cultivation of control materials uniformly failed to yield growths of this organism. The materials tested consisted of the unfiltered and filtered nasopharyngeal washings of persons free from influenza, some of whom were suffering with acute coryza, the lung tissue of normal rabbits and of rabbits with bacterial respiratory infections, and the uninoculated media.

The intratracheal injection in rabbits and guinea pigs of mass cultures of this organism has induced effects on the blood and lungs of these animals which are not to be distinguished from those obtained with the nasopharyngeal secretions of patients in the early hours of epidemic influenza. From the pulmonary lesions thus induced, the same organism has been recovered in pure culture, and has been found to cause similar lesions on subsequent animal passages. Its pathogenicity is not lost by prolonged artificial cultivation.

Our experiments indicate that the cultivable bodies obtained directly from human nasopharyngeal washings and from affected rabbit lungs are strains of the same organism. This organism appears to be the source of the reactions which occur in experimental animals—rabbits and guinea pigs—as a result of the intratracheal injection of nasopharyngeal washings obtained during the early hours of uncomplicated epidemic influenza in man.

Other investigators have not found the *pneumosintes* with equal regularity. Detweiler and Hodge,[28] of the University of Toronto, examined six cases of influenza for *pneumosintes* and found them in three. Their conclusions are given in their own words:

1. Six cases of epidemic influenza in various stages of disease were investigated.

2. Suspicious cultures of bodies resembling *Bacterium pneumosintes* were obtained in three cases, twice from the lung filtrates of inoculated animals and once from the filtrate of nasopharyngeal washings direct.

[28] Detweiler, Herbert K., and Hodge, W. R.: An attempt to isolate a filter-passing virus in influenza. Jour. Exper. Med., January, 1924, XXXIX, No. 1.

3. In three instances material was obtained within 36 hours of the acute onset, thus confirming the observations of Olitsky and Gates.

4. Macroscopic and microscopic findings in the lungs of inoculated animals were uniformly negative.

Lister [24] cultivated on Smith-Noguchi medium an organism corresponding to *Bacterium pneumosintes* and recovered it in nasopharyngeal washings from a volunteer who was taken sick with influenza following inoculation.

In January, 1920, Maj. H. J. Connor,[25] United States Army, concluded that in the locality of United States Army General Hospital No. 19 there was a direct relationship between the *Streptococcus hæmolyticus* and the influenza epidemic. The findings of *Streptococcus hæmolyticus* were always antecedent to those of *Bacillus influenzæ*, which organism is the primary infecting agent.

A vaccine from *Bacterium pneumosintes* was tested by Maj. H. J. Nichols,[26] of the Army, in 1922–23, with the result that slight protection was observed, but with the dosage used vaccine *pneumosintes* did not produce real protection. In the words of this investigator:

> The general conclusion is that the results are not decisive, as there were not sufficient cases, but several cases of influenza did occur among the vaccinated; and this evidence, with that at Fort Myer, leads to the final conclusion that, with the doses used, vaccination with *B. pneumosintes* did not produce any clear-cut protection against influenza.
>
> In view of our imperfect knowledge of the new group of organisms of which *B. pneumosintes* is a member, it is premature to draw any final conclusion from this vaccination experiment as to the etiology of influenza. The persistent work of the investigators at the Rockefeller Institute has revealed a new group of organisms which can be handled only with laborious technique. The key to the influenza problem very probably lies in this group; but further work is necessary, and at the proper time further cooperative work should be undertaken by the Army.

As a rule, however, *pneumosintes* has not been found by the majority of laboratory workers. Rosenow,[27] of Rochester, advances the suggestion that there is a definite relationship between the etiology of encephalitis and influenza. In the report of a case supporting this view he says:

> The patient contracted influenza during an epidemic wave of the disease, with which his entire family had been ill, at a time (1920) and in a region in which the green-producing streptococcus was found prevalent and with which I produced the symptoms and lesions of influenza in guinea pigs. The streptococcus isolated from the patient's throat several months later, during his

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[24] Lister: South African Medical Record, 1922, No. 22, p. 434.

[25] Connor, H. J.: The incidence of *Streptococcus hæmolyticus* in a recent epideemic of flu. Jour. of Lab. and Clin. Med., 1920, 5: 12: 767.

[26] Nichols, H. J.: Report on vaccination against influenza in the Army with *B. pneumosintes*, 1922–23. The Army Medical Bulletin, Medico-Review Section, Oct. 15, 1923.

[27] Rosenow: Changes in streptococcus from encephalitis, induced experimentally and their significance in pathogenesis of epidemic encephalitis and influenza. Jour. of Inf. Dis., Vol. XXXIII, December, 1923, p. 206.

attack of encephalitis, resembled morphologically, but not in virulency, the one isolated so commonly during the pandemic of influenza. Results on intratracheal injection in guinea pigs were similar to those observed in the experiments with the green-producing streptococcus from influenza. * * * According to the results of these experiments the same streptococcus may give rise to these widely different diseases, depending on whether it be in the virulent or pneumotropic phase, when influenza would result, or in the less virulent but neurotropic phase, when polioencephalitis and allied conditions would be prone to develop.

Since the changes induced in the microorganism include alterations in morphology, cultural characters, infecting power, and immunologic state similar to those noted in my studies and those of Clough on mutations in the pneumococcus-streptococcus group, and to those noted by Walker in the case of hæmolytic streptococci, might it not be that members of this group of organisms to which this strain belongs, which are normally present in the upper respiratory tract of humans, acquire under certain conditions these and other phases in their life cycle and thus afford explanation for the occurrence of sporadic cases and the origin of epidemics in isolated regions?

The bacteriologic findings in groups of influenza cases have filled the literature. A few will be given to illustrate the great diversity of opinions: C. L. Sherman,[28] of Minnesota, says:

Jundell, of Stockholm, states that during the last seven years he found the influenza bacillus in about 10 per cent of the cases in which a clinical diagnosis had been made. Ruberman, in a typical influenza epidemic, found the organism in only 6 per cent of the patients examined.

From a review of the literature we find that the influenza bacillus is no more prevalent in the so-called epidemics of influenza than in ordinary catarrhal infections would suggest that possibly the organisms are simply secondary invaders to other forms of infection.

The streptococci being found in pure culture in the majority of epidemics of so-called grippe, while the influenza bacillus is only occasionally demonstrated, would justify the assumption that the majority of these outbreaks are some form of streptococci infections.

Ivan C. Hall,[29] after examinations of 33 specimens from 25 persons suffering from rhinitis, draws the following conclusions:

1. No anaerobic spirochete described by Tunnicliff was seen.

2. Probability of obligate anaerobes developing in the respiratory tract seems slight, in view of the excessive air supply, and the above findings indicate that such infections occurred, if at all, only infrequently in the cases of respiratory diseases presented for examination during the winter and spring season of 1920.

3. There was nothing to show that the obligate anaerobic coccus found in one instance was pathogenic.

In 1915 Luetscher,[30] of the Johns Hopkins University, in his studies of some 600 cases of nontuberculosis infections of the respiratory tract, found the pneumococcus as the cause of 62 per cent of

[28] Sherman, C. L.: The Lancet, 1913, XXXIII, 666.

[29] Hall, Ivan C.: Influenza studies—Search for obligate anaerobes in respiratory infections—An anaerobic micrococcus. Reprint from Jour. Inf. Dis., February, 1921, XXVIII, p. 127.

[30] Luetscher, J. A.: Bacteriological and clinical study of the nontuberculosis infections of the respiratory tract. Archives of Inter. Med., 1915, XVI.

the infections below the larynx, and the influenza bacillus in 29 per cent. The two organisms cause 91 per cent of the infections of the bronchi and lungs, 74 per cent of the infections of the larynx, and 31 per cent of the infections of the nose, throat, and sinuses.

Dr. E. O. Jordan [31] in 1919 made an intensive examination of patients from the Students' Army Training Corps of the University of Chicago, university students, and civilian patients. His conclusions are:

Groups of individuals who have been more or less in intimate contact with one another may harbor very similar assemblages of microorganisms, but differing from other groups examined at the same time.

Two organisms most commonly and abundantly present are Pfeiffer's bacillus and Mather's diplococcus and streptococcus.

Pfeiffer's bacillus was found in 64 per cent of influenza cases and in larger numbers at the end of the attack.

Mather's coccus was found about as frequently and abundantly as Pfeiffer's bacillus, and its association with the pneumococcus is closer.

Heavy infections of Pfeiffer's or Mather's has no influence on cases with scant infections. In other words, patients with heavy nose and throat infections showed no increased degree of sickness over those in which the infections were light.

In his report to the Director General of Medical Services, Ottawa, Lieutenant Colonel Parsons [32] gives the number of times each infection was present either alone or associated with others:

Swabs from nasopharynx gave:

Bacillus influenzæ	87
Streptococcus	136
Pneumococcus	136
Micrococcus catarrhalis	36
Staphylococcus	30
Bacillus of Friedlander	24

Bloomfield [33] discusses the etiology of colds, in which he links the common cold rather closely with influenza, grouping cold into three groups; e. g., (1) the common cold, (2) true pandemic influenza, and (3) so-called grippe, intermediate in severity between colds and influenza. He also mentions the characteristics which these conditions have in common. His discussion is as follows:

In summary, then, a consideration of the clinical feature of colds, together with the information available in the literature, leads to the following conclusions:

1. That the common cold is a definite disease generically related to grippe and influenza. The primary disease is often followed by local complications which tend to overshadow the picture.

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[31] Jordan, E. O.: Observations on bacteriology of influenza. Pub. Health Rep., June 27, 1919.

[32] Parsons, H. C.: Canadian Medical Association Journal, Vol. IX, 1919.

[33] Bloomfield, Arthur: Variations in the bacterial flora of the upper air passages during the course of common colds. Johns Hopkins Bulletin, 1921, Vol. XXXII.

2. Cold may produce disturbances in the upper air passages which are to be distinguished from true infectious colds.

3. None of the common bacteria found in the nose or throat have been proved to be the primary cause of colds.

4. The most convincing evidence in the literature favors a filtrable virus as the cause of the common cold.

With the knowledge previously gained of the normal throat flora as a background, the present 10 cases were studied to determine any variations from the normal which might occur during the course of a cold and to see if such variations might be interpreted in such a way as to shed light on the etiology of the disease.

In the uncomplicated cases the outstanding fact was this, that the flora differed in no fundamental way from that which obtains in healthy individuals. As in normal controls, nonhæmolytic streptococci and Gram-negative cocci are constantly present. As in the normal, there is a shifting transient flora consisting of various organisms—diptheroids, coarse Gram-positive cocci, minute Gran-positive organisms, white staphlococci, and others. Two points in regard to this transient flora are, however, worthy of note. It is distinctly richer and more varied than that found in our series of controls, and in some cases organisms persisted for considerable periods of time, as in the case of the yeast infestation in E. A conceivable explanation of these findings is that the disturbance of the mucous membranes during the cold allows a general increase in the activity of bacterial growth on these surfaces. This fits in with the old theory that the cold, whether produced primarily by cold or by infection, leads to environmental changes which, as it were, light up the bacterial flora already present in the mouth. However, we feel definitely that none of these organisms can be the primary cause of the cold, because their presence is too variable and inconstant, and the variety of them is great.

The almost constant presence of hæmolytic influenza bacilli was of interest. These organisms were absent in only one case of the series. At first one was tempted to relate them to the cold in an etiological way, but it soon appeared that they could be nothing more than saprophytes, inasmuch as they were present in equal numbers in unaffected controls. Their frequency, however, illustrates one of the grave pitfalls of respiratory bacteriology. * * *

On clinical grounds the view was advanced that the common cold is an infectious disease analogous to influenza, featured by the frequent development of complications in the upper air passages, such as sinus infections, tracheitis, and otitis. A review of the literature showed no convincing evidence that any known organism is the primary cause of cold.

The cultural studies in the present report fail to show in uncomplicated cases any variation in the flora which would enable one to select any organism or group of organisms as the cause of colds. On the other hand, where clinical complications occurred, pathogenic organisms were definitely associated with them.

We feel, therefore, that the primary cause of colds is probably an organism as yet unknown and certainly not one of the usual pathogens such as streptococcus, pneumococcus, *B. influenzæ*, or staphylococcus. But the primary cold, whatever its final cause, alters the mucous membranes in such a way as to allow secondary bacterial invasion and constant consequent frequent development of local complications. The cultures clearly indicate that such complications are due to a variety of bacteria, such as pneumococcus, streptococcus, and staphylococcus.

In general, it seems that the method of serial comparative study is necessary in working out the bacteriology of respiratory infections. Such a method

allows one to pick out and interpret the significance of unusual organisms, and also checks premature conclusions as to the etiological bearing of such organisms.

In summary, then, the common cold falls into a rather sharply defined group of diseases including (1) the common cold, which is endemic and at times mildly epidemic; (2) true influenza, which is pandemic; and (3) so-called grippe, intermediate in severity between the common cold and influenza, and usually occurring in mildly epidemic form. All these diseases have the following characteristics:

1. There is a primary disease manifested by a constitutional reaction and by hyperæmic phenomena in the upper air passages.
2. The uncomplicated disease is of self-limited duration.
3. There is usually leucopenia or at least an absence of leucocytosis.
4. Spread of the disease seems to be mainly by direct contact.
5. There is a remarkable tendency to complications in the respiratory tract; in the case of colds, to localized infections, such as otitis, sinusitis, laryngitis, and bronchitis; in influenza, to broncho-pneumonia as well.

Our purpose in presenting this clinical analysis is to bring out clearly the fact that the common cold is a definite disease of fixed characteristics, to be distinguished sharply from complications which frequently occur during its course. This fact, as well as its striking resemblance to a group of diseases of unknown etiology, should make one cautious in accepting any of the obvious organisms of the throat as its cause.

It is a well-known fact that organisms which may produce infections of the nose and throat are constantly found in those localities during health. The supposition naturally follows that, due to some change in the nose and throat, or due to so-called lowered resistance, the germs already prevalent multiply to a degree of toxicity and infection results. The work of Mudd, Grant, and Goldman[34] is of intense interest in demonstrating that actual physical changes do occur in the mucous membrane of the nose and throat reflexly from thermal influences applied to remote parts of the body. These investigators subjected volunteers to chilling (applications of wet towels and electric fan to back), taking temperature of the mucous membrane and skin. They describe their work as follows:

With the start of this process a marked depression, both of mucous membrane and temperature, begins. The maximum fall of mucous membrane temperature is 1.42° C., reached in 18.4 minutes. The synchronous point on the skin curve represents a drop of 1.73° C. The curve (skin) falls away a little more sharply than the mucous membrane curve. We should expect on mechanical grounds this difference in the curves, for the more exposed forehead would, of course, lose heat more readily than the mucosa of the palate and pharynx. When it was seen that the mucous membrane temperature had ceased to fall, the fan was turned off and the subject again wrapped. Here a disparity in the behavior of skin and mucous membrane vessels appeared. The skin temperature climbs steeply and surmounts the level at which chilling begins. The skin "reacts," as is commonly said, but the mucous membrane temperature rises only 0.73° C. Its maximum recovery is reached after 12.7 minutes and is 0.69° below the last point before chilling. During the remainder of the 3.5

[34] Mudd, Stuart, Grant, S. B., and Goldman, Alfred: Annals of Otology, Rhinology, and Laryngology, Vol. XXX, No. 1, March, 1921.

minutes of observation it falls 0.21° C. We are forced to conclude, therefore, that the vaso constriction and ischemia reflexly produced in the palatine and pharyngeal mucous membrane by chilling the body surface persists in part for some time, at least.

These investigators chilled the feet of volunteers and obtained a lowering of mucous membrane temperature of 0.29° C., but no effect on the skin of the forehead.

It is a fact beyond question that potentially pathogenic bacteria may lead a saprophytic existence upon the pharyngeal and tonsillar mucous membranes of healthy subjects. It is equally indisputable that those bacteria may, under appropriate circumstances, become the active agents of infection, local or generalized. We believe that exposure to cold may be one such exciting factor of infection. We have shown also that chilling of the body surface causes a reflex vaso constriction and ischemia in the mucous membrane of the nasal cavity, postnasal space, orapharynx, palate, and tonsils. That the latter is the mechanism by which local resistance is lowered and infection excited, we have not proved. However, there would seem to be justification for advancing, tentatively at least, the hypothesis that the ischemia may mediate the infection.

Prior to these experiments, Jonathan Wright[35] suggested that such changes might be the result of such influences, in this wise:

It may well be, as has been admitted, that certain bacteria are at once pathogenic when they reach the mucous membrane. Indeed, this seems very probable when they reach the mucous membranes of certain individuals. It may well be that such individuals always present, owing to systemic states, conditions of the mucosa which offer an ever-open avenue to infection; but, granting all this, which, indeed, is in reality a part of our conception of the mechanism of the process, it seems extremely likely that local biochemical change dependent upon molecular activities acting through the sympathetic nerves may be set up by external or internal agencies, by the chilling of the body surfaces, or by derangements in the activities of the internal organs. Owing to the fact that wet feet and the chilling of distant regions of the surface of the body are, at least in clinical experience, quite as frequently followed by coryzas and sore throats as the direct impact of such external influences upon the head and neck, we have the right to infer that the shock at the surface must be transferred to internal nerve ganglia and there translated into impulses which are carried to the surfaces of the mucosa of the upper air passages. There they give rise to the chain of biophysical and biochemical changes which may simply result in a mild or a catarrhal pharyngitis, the resolution of which terminates the chain, or these conditions may themselves be the starting point of bacterial invasion.

Coincident with these bacteriological investigations and the intense experimentation in efforts to link influenza and the common cold with a definite bacteriologic agent, theories are advanced by other investigators in which other influences are suggested as the primary cause. In this era, as in olden times, these conclusions are based on weather influences.

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[35] Wright, Jonathan: Annals of Otology, Rhinology, and Laryngology, 1914.

In this connection, an epidemic of influenza in the Eighth Corps Area, at San Antonio, Tex., has been described as follows by Lewis B. Bibb[36] in the Military Surgeon:

1. Periodic seasonal outbreaks of acute respiratory disease have occurred in the military population in and around San Antonio, Tex., for the past five years. The epidemic of 1923 comprised 891 cases.

2. In certain instances the epidemic has supervened upon or become worse after a spell of cold or wet weather.

3. Several organizations have shown simultaneous beginning of outbreak.

4. Eighty per cent of 252 consecutive cases gave a history of recent exposure to dampness, lowered temperature, or other adverse influence.

5. The onset was usually sudden, with cough, chill, and aching.

6. Rales occurred in 61 per cent of cases; were present at onset in about one-half of these; average duration of rales, four days.

7. The moderate leucocytosis was usually seen, especially affecting the polymorphonuclear leucocytes.

8. No deaths occurred, no complicating empyema, and only three cases of broncho-pneumonia.

9. The patients concerned in this epidemic usually became afebrile after two to four days and had a prompt and uneventful convalescence.

Conclusions:

1. The symptoms of 891 cases of acute bronchitis constituting an epidemic could have been caused either by bacterial infection, by exposure to lowered temperature, or other adverse influences.

2. Empyema did not occur; purulent sinusitis was very rare; the epidemic was characterized by a dearth or absence of positive signs of localized bacterial invasion.

3. The distribution and dates of onset indicated that the majority of cases (80 per cent) were provoked rather than transmitted cases.

4. The onset following so promptly after exposure to lowered temperature affords evidence that the early phase of the attack is not due to bacterial activity, but is due almost solely to the excessive reactivity of the economy toward the injuriously physical or other equivalent influence.

5. The prompt subsidence of the attack renders it unlikely that bacteria are a complicating factor during the late phases.

6. The view is advanced that normal vasomotor tone is possible only in the presence of a mixed shower of sensory impulses comprising discharges from the neurones mediating warmth as well as discharges from the neurones mediating coolness, and that an unfortunate sequence of stimuli can lead to dissociation of these two varieties of impulses and set up disturbances in blood distribution and heat regulation with their consequences.

Another opinion implicating the weather is advanced by O'Connell,[37] of London, who arrived at some very interesting conclusions. This author attributes influenza to the weather. He says:

The injection of even as small a quantity as 6 c. c. of pure distilled water into the blood produces a rise of body temperature which in some persons reaches 37.8° C. (100° F.). Such a rise of body temperature quickly disappears on health and the temperature returns to normal. The explanation of this rapid rise of temperature is that the addition of even this small quantity of water to

[36] **Bibb, Lewis B.: Predominance of nonbacterial over bacterial etiology in 891 cases of epidemic respiratory disease. The Military Surgeon, January, 1924.**

[37] O'Connell, M. D.: The Practitioner, London, June, 1919, CII, p. 302.

the blood increases the chemical changes that produce heat in the body. When a cool and moderately damp atmosphere becomes very damp one of its effects is that it causes a retention of water in the blood and tissues of the body, and consequently an increase in the chemical changes that produce heat in the body; hence I suggest that when influenza is epidemic the explanation of the fact that some are immune and others suffer from the disease in different degrees of severity is afforded by the different proportions of water which are found in the blood and tissues of different individuals in health. All have not exactly the same proportion of water in their blood and tissues in health.

Craft,[38] of Chicago, thinks that influenza is due to a chemical agent in the atmosphere. He reviews the bacteriological literature of influenza and points out that no one organism can be considered responsible. He does not accept the views that organisms are the prime factors, because (1) of the extreme rapidity with which the disease spread over the globe at a time when ocean-going traffic was virtually at a standstill; (2) because of the nature of the disease, which appears to assume the characteristics of some chemical poison. Indeed, he says it may be likened in many ways to "Caisson disease." His discussion is as follows:

I hold that a chemical agent in the atmosphere is responsible for the primary initiation that paves the way for the bacterial infection. Now, let some one prove the fallacy of this theory. Our scientific brothers call it contagium, while it has traveled faster than the crow flies—yet who infected the Eskimos in the inaccessible far north or inhabitants of countries in the far south end of the globe at the same time as Europe and America?

Richter,[39] of San Francisco, in a voluminous discussion, advances the anticyclonic theory as the prime etiological factor in influenza. He says:

Anticyclones are found in the rear of extensive cyclones by the discharge of immense cold masses of air into lower latitudes forming areas of high pressure. If the cyclone ahead of this area retards its procession, then a more or less stationary anticyclone is found.

The very source of the pandemics is found to be in that part of Asia Minor or North America on the Northern Hemisphere where the centers of highest pressure are located on those parts of the continents. The air, carried by such dynamic anticyclones * * * is distributed with a velocity equal to that of our railway trains.

The cycles in which the pandemics alternate with periods of relative quiescence are distinctly covered by the cycles of high air-pressure periods during and before the pandemics and of low pressure following them. The influenza pandemic extends and spreads in the same direction and with the same velocity as the great anticyclone spreads from its center over a continent. In the United States, therefore, it generally attacks first those districts that lie in the path of the Alberta type or Hudson Bay type.

We have reason to believe that air of some anticyclones contains ozone in unusual quantity as a product of unusual solar output. If we hesitate to

[38] Craft, A. J.: Is epidemic influenza of bacterial origin? Am. Jour. of Clin. Med., 1919, XXVI, p. 279.

[39] Richter, C. M.: Influenza pandemics depend on certain anticyclonic weather conditions for their development. Arch. of Int. Med., Mar. 15, 1921.

deduce that ozone is causative of influenza because its odor and the gas itself has not been detected in the air we breathe during a pandemic, we must admit that no attempt has been made to find it.

H. H. Roberts [40] believed cats and dogs to be responsible agents in the spread of influenza, and summarized his belief as follows:

Careful investigation of a great number of cats and dogs has demonstrated that 90 per cent of these animals are infected with a specific bacillus producing a distemper of contagious form of nasal catarrh. I have found in a number of instances where persons have been troubled with a stubborn rhinorrhea of many months' duration there is present the specific organism which is characteristic of the disease as found in cats and dogs. * * * I am quite positive, after serious study, that cats and dogs are largely responsible for the epidemic of colds and chronic catarrhal rhinorrhea which infect great numbers of the populace.

Friedman [41] believes that the bedbug is responsible for the spread of influenza, and makes positive statement to that effect, but offers no proof.

Corpet and Dwight [42] believe that the eye is the portal of the infecting agent, as shown in the following summary:

The eye must be considered as the important portal of infection in respiratory diseases, and although the greater part of the infectious material entering by way of the eye is subsequently swallowed and passes into the gastrointestinal tract, a small but definite portion of it finds its way into the larynx and trachea, where it may persist even as long as a week.

The contention of Park [43] as to known proof of the Pfeiffer bacillus being the cause of influenza is given in the following:

The prevalence of influenza bacilli, in many cases showing no symptoms, makes it difficult to consider all cases having the symptoms of influenza with the presence of influenza bacilli as being due to them.

In conclusion, the following quotation from Osborne,[44] of Yale University, is given:

While congestion of the mucous membranes of the upper air passages may simulate colds, probably all so-called colds are due to infection. * * * Evidently there are other germs which rapidly spread contagion that have not yet been discovered.

This brief summary of the opinions of the profession regarding influenza and the common cold is merely indicative that as yet we are still uncertain as to what is the cause of these conditions. It is of interest to note here that observers, when mentioning the "common

[40] Roberts, H. H.: Dogs and cats as source of epidemic coryza. N. Y. Med. Jour., 1919, Vol. CIX, p. 186.

[41] Friedman, G. A.: Possible spread of the flu through the bedbug. Med. Record, N. Y., Jan. 4, 1919, p. 95.

[42] Corpet and Dwight: The eye as a portal of infection in respiratory diseases. Jour. A. M. A., Feb. 21, 1920.

[43] Park, W. H.: Bacteriology of influenza. N. Y. Med. Jour., 1917, Vol. CV, p. 529.

[44] Osborne, Oliver T.: Etiology and treatment of colds. N. Y. Med. Jour., 1919, Vol. CIX.

cold" in connection with influenza, studiously attempt to separate the two conditions into their respective entities, showing by this very action intimacy between influenza and colds, both etiologically (so far as is known), and in the general behavior of the two conditions. The evidence, at least as far as the work done on the etiology of colds and influenza shows, would tend rather to bring these two diseases into more intimate relationship than to separate them.

Epidemiology.

The literature on the epidemiology of influenza and the "common cold" appears as voluminous as, if not more than, that on the etiology of these conditions. The wide diversity of opinions by observers of equal rank and reputation in the medical world shows that as yet there is a lack of definite knowledge regarding the fundamental factors in the epidemiology of the disease. It is generally accepted that influenza and the "common cold" are very contagious and are produced by contact, although even the latter assumption is not concurred in by many.

As mentioned before, earlier observers from the time of Hippocrates laid great stress on meteorological and natural phenomena as a tangible thing upon which they could connect periodic reappearances of the "plague." As stated, these phenomena varied from changes of winds and the appearance of comets to mighty upheavals caused by earthquakes. A few personal observations as expressed by the writings of some who have studied the question are interesting and will be quoted. Dr. Thomas Short,[45] of London, made the following observations in 1750. Undoubtedly what he described was influenza:

> There is a disease which once in four or five years has a more general and remarkable run. Of all common epidemics it attacks most suddenly, unexpectedly, generally makes the shortest stay and greatest havoc in a little time of weak, declining, consumptive, and asthmatic constitutions; of the aged and children, chiefly and mostly; and yet there is a very small proportion between the infected, or such as are seized with it in one shape or another, and those that die of it. It is also immediately succeeded by as healthy a time, carrying off chiefly some almost worn-out constitutions that would not have survived long had not it come. I mean catarrhs and ephemeras. They depend immediately on the preceding state of the air and weather, and at different times are found to require various methods of cure, according to the late and present constitution of the season, which difference consists chiefly in the advantage or disadvantage of bleeding, a case only to be resolved by observation, not theory.
>
> We see—
>
> 1. That this disease, of all epidemics, common to all ages and sexes, comes oftenest, has the most extensive spread and general infection of all others.
>
> 2. Varies most in its degree of mildness and severity, as from a little sneezing, heavy-headedness, an hour's easy sweat after a slight shivering, or an hour's running at the nose, to a high degree of fever, delirium, and death.
>
> 3. It differs also in its manner of seizure, symptoms, and duration.

[45] Short, Thomas: Bills of mortality, London, 1750, p. 221.

Heberden,[46] in describing what he calls an "epidemical cold" in London in June and July, 1767, unquestionably is describing influenza, which he notes as a condition which resembles a "common cold," but which differs in severity of symptoms. He states:

In the very beginning of June, if not sooner, a few persons in London were affected with several symptoms of a cold, which of their own accord they in two or three days observed to differ from a common cold, and to resemble the epidemical one of the year 1762, on account of its being attended with a greater languor, feverishness, and loss of appetite than what the same degree of such a complaint usually brings on.

About the middle of June the same disorder began to be much more common in London and was manifestly epidemical. It was at its height about the last week in June and beginning of July and before the end of July had entirely ceased.

The symptoms were a shivering which returned frequently for the first two or three days; a troublesome and almost unceasing cough, at least for the first day or two; very acute pains in the head and back and abdomen, particularly just under the left ribs, piercing them and into the back; occasionally want of sleep. All these symptoms did not attend the same person, but most of them had at least one of them. Lassitude, loss of appetite, and fever belonged in some degree to all.

In some this disorder began like something worse than a common fever, and in a day or two seemed slighter than a common cold; but many of the symptoms hung upon several at least for a week, and sometimes lasted for a month. When its attack was most violent, it brought on anginas, pleurisies, and peripneumonia, with continual fever. Where its attack was a little greater, the fever, though great enough at its height to bring on deliriousness, yet had plain remissions or intermissions.

It attacked equally both sexes and all ages. I saw some infants ill of it, and it appeared to be fatal to a very few old and infirm persons; but, in general, it was less epidemical and far less dangerous than the cold of 1762.

This epidemical illness bore bleeding very well, for it was plainly of the inflammatory kind, by bringing on, where it was most excessive, inflammations of the throat and pleura and lungs and such as sometimes required bleeding to be repeated. When, after bleeding or of itself, it turned to an intermittent, the bark took place and made an effectual cure. These two remedies, together with a few others for the relief of some incidental symptoms, were all which it seemed to want where it was bad, but in the generality of people it was left to nature and cured itself.

The season preceding this disorder was only remarkable for being unusually cold; but then it is observable that the similar epidemical cold of the year 1762 was preceded by weather as uncommonly warm.

As the same disorder was reported to be common about the same time in many other parts of England, and more fatal than it was in London, it is very desirable that the physicians of those places would favor the college with what they observed relating to its history and cure.

Though this epidemical illness be just over, yet there seems no reason to apprehend any of those lasting ill consequences from it which attended the sufferers in 1762, many of whom continued in a languishing state for several months, and then died; and others complained for two or three years that its ill effects still hung upon them, and that they had not, in all this time, recovered perfectly from the hurt which it had done their constitutions.

[46] Heberden, W.: The epidemical cold in June and July, 1767. Med. Trans. Roy. Coll. Phys., London, 1785, iii, p. 437. Read at the college, Aug. 11, 1767.

Controversies have waxed strong regarding what rôle, if any, the weather may play in the epidemiological spread of influenza. This fact has been mentioned previously under the discussion of etiology, in which it was seen that positive statements had been made as to this influence. Going back to 1784, Gray,[47] of London, offers the following:

But though the idea that the influenza originated in this part of the world from changes in the sensible qualities of the atmosphere can not be admitted, it must be allowed that the state of the weather may have had some power in altering or aggravating its symptoms; yet the instances above mentioned of changes in the weather without any alteration being perceived in the disease gives reason to doubt whether that power was so great as some have supposed it; and with respect to the weather previous to the appearance of the influenza, it is remarkable that, though in most parts of England it had been uncommonly cold and wet, it had in other parts of the world where the disorder was equally general been equally dry. Upon the whole, the progress of the disorder is certainly more easily explained upon the supposition that it was propagated by personal communication than by any other that has been suggested.

In a letter from Dr. R. Hamilton of the Royal College of Physicians and Surgeons, to Doctor Lettsom in 1787 appears the following:

We have many examples to prove that the air can not hold nor yet convey contagion to any distance. If it be mixed with the atmospheric air, it is soon dissipated, perhaps chemically decomposed, if it be a compound body, and its nature altogether changed. Experience shows that contagions have always been communicated by contact with the infected, either mediately or immediately—i. e., by persons who bring it on their clothes to the persons who receive it—or by its being conveyed from the infected in various kinds of goods.

Bad weather may and often does act on the human body so as to debilitate it, by which it becomes more disposed to receive any disease that rages at that time.

In Hirsch's Handbook the following observers are listed as *not* considering influenza to be an air-borne disease:

Whytt for the Edinburgh epidemic of 1757.
Baker for the London epidemic of 1762.
Fothergill for the Northhampton epidemic of 1775.
Barclay for the St. Thomas epidemic of 1823.
Ward for the Penang epidemic of 1831.
Lombard for the Geneva epidemic of 1831.
Berndt and Dieterich for the epidemic of 1833.
Greenhow and Graves for the English epidemic of 1837.

The following is quoted more in detail from Baker.

If, indeed, the disease in question at present owed its origin to those peculiarities of the weather which are perceptible to the senses, how did it happen that people who were contiguous in locality did not fall ill about the same time?

[47] Gray, E.: An account of the epidemic catarrh of the year 1782. Med. Communical, London, 1784, i, pp. 1–70.

How did it happen that the disease attacked those who were separated not more than 2 miles from this city with much more severity than the Londoners themselves? What may we consider to be the reasons why it invaded the city of Edinburgh early in May, but certain parts of Cambria, near by, not until late in June? Certainly, whatever we are permitted to know about the whole subject is extremely limited.

Hirsch concludes his discussion on the influence of the weather by the following paragraph:

I have thought it necessary to discuss the foregoing question somewhat fully, inasmuch as even at the present day there are still many voices raised, and influential voices, too, against the specific character of influenza, and in favor of its identity, both in etiology and in pathology, with epidemic bronchial catarrh. I can not conclude this section more suitably, perhaps, than by adducing the opinion arrived at by the Wurtemberg physicians in the course of an investigation into the influenza epidemics of that kingdom in the years 1831–1858: "It appears from these researches," runs the report, "that influenza prevailed sometimes in summer, sometimes in winter; sometimes in unusually warm weather, and sometimes in unusually cold; sometimes in dry weather, sometimes in wet. Considering, further, that the weather had thousands of times shown the same character as in influenza years, without influenza prevailing, and that influenza is usually prevalent at one and the same time over the whole of Europe and even in other parts of the world, where we may safely conclude that the weather had been of all kinds, we are constrained to admit that influenza is altogether independent of weather conditions. Should we desire, however, to open up the further question of an influence exerted by agencies or substances such as the electricity of the air, ozone, and the like, we should be well advised to wait for further observations before taking the trouble to discuss it.

Continuing, Hirsch makes some very interesting observations in which he links up the common bronchial catarrhs, which so often are the same as common colds, with influenza. In his own words:

The alleged endemicity of influenza also, in several countries situated within the cold zone, reduces itself, according to the data of Schleisner, Hjaetelin, and Fuisen for Iceland, of Panum for the Faroe Islands, and of Lange for Greenland, to the question of whether influenza may not have been confused with the bronchial catarrhs that occur every year in wide distribution in these countries in spring and autumn, influenza itself being not really more frequent than in other latitudes. But influenza shows the same independence, as regards its origin, of the seasons and of the influences of the weather; and it is in that respect that it is marked off most essentially and most decidedly from bronchial catarrh.

Hirsch believes influenza to be *infective*, but does not think that it is at all communicable or contagious—an interesting deduction by an authority of rank and reputation. He says:

Influenza is a specific *infective* disease, like cholera, typhoid, smallpox, and others, and it has at all times and in all places borne a stamp of uniformity in its configuration and in its course such as almost no other infective disease has. * * * These considerations, taken along with peculiarities in the incidence and course of influenza epidemics—their occurrence suddenly and

without prelude and their attacking the people en masse; their equally sudden and complete extinction after a brief existence, generally of two to four weeks, and the frequent restriction of the disease to one place, while the whole country round has been completely free from it—all these points are so foreign to the mode of development and the mode of spreading proper to such maladies as originate beyond doubt through the communication of a morbid poison that we shall find it hard to discover any reason for counting influenza among the contagious or communicable diseases.

One of the reasons for doubting the contagiousness of influenza has been the reported instances from time to time of the sudden occurrence of influenza among persons on ships in mid-ocean, clearing from ports where no influenza was known or prevalent at the time of departure. Hirsch submits the following report:

In September, 1781, influenza attacked the crew of an East Indianian on the voyage from Malacca to Canton so generally that scarcely a single person escaped; when they left Malacca the disease was not prevalent there, but when they arrived at Canton it transpired that their outbreak on board in the China Sea had happened at the very time when the disease was showing itself with equal intensity at Canton.

Reynolds [50] comments on this report in this wise:

The statement that influenza will thus break out in mid-sea, without there being any possibility of the disease having been introduced on board, is a most important piece of evidence, as it would prove that the atmosphere can not only carry the poison, but that no degree of dilution can destroy it without denying the occurrence of such outbreaks. I can not but consider we require better evidence of ships being attacked in mid-ocean. In some of the quoted instances the ships had been at a port either known to be infected or in which influenza was really present, *though it had not become epidemic*. As we are ignorant of the exact period of incubation, some men may have been infected before sailing. In other cases the examples are of old date, and it is impossible to feel quite sure that the evidence is correct—such, for example, as the celebrated case of the *Atlas*, East Indianian, which was attacked with influenza on a voyage from Malacca to Canton, Malacca being healthy at the time, but Canton being affected at the same time as the ship.

To bring this discussion to a more modern date, the following interesting information is quoted from a report [51] of a slight epidemic of influenza in Sitka, Alaska, in 1924:

Members of the crew of two or three fishing vessels informed me that their illness started while at sea and after they had been at sea for a week or longer.

The question of temperature as an epidemiological factor is discussed by Reynolds as follows:

Owing to the confusion in the popular mind between influenza and common catarrhs or catarrhal fevers, it has been always a common opinion that influenza depends either on a low temperature or a sudden variation of temperature. This error has taken a long time to kill, but almost every writer since

[50] Reynolds, J. Russell.: A system of medicine, Vol. I.
[51] Letter from U. S. Public Health Service physician to the present writer.

the epidemic of 1580 has examined this point and has decided that there is no connection between either low temperatures or variations in temperatures and influenza. The following observers hold to this opinion:

1. Salius Diversus (1580).
2. Molineux (1693).
3. Whyatt (1757).
4. Baker (1762).
5. Haygarth (1775–1782).
6. Fothergill (1775).
7. Metzger (1800).
8. Lombard (1831).

One of the first efforts to obtain epidemiological data following an epidemic of influenza was made by Dr. T. Thomson [52] in the epidemic in Great Britain in 1836–37. Questionnaires were sent out by a council of the Provincial Medical Association of London to doctors throughout Great Britain. Following is the questionnaire with a résumé of the replies:

1. When did the influenza appear in your neighborhood? How long did it prevail there?
   (Various dates given from November to February—generally January 3 to 13 were dates given.)
2. Did it attack a great many individuals at the same time?
   (Replies uniformly in the affirmative.)
3. Did it appear partial to any age, sex, or temperament, or did it appear to attack all indiscriminately?
   (Over one-half answered the last half "Yes"—some say adults more susceptible than children.)
4. Was it milder when it attacked children?
   (Three-fourths replied "Yes.")
5. What age appeared to suffer most from it?
   (Almost all replied aged suffered most.)
6. Was the spread of the distemper very extensive in your neighborhood?
   (Uniformly "Yes.")
7. What was the proportion of deaths to the numbers attacked?
   (One in 42, or 2.3 per cent.)
8. What circumstances predisposed the patients to a fatal termination of the disease?
   (Old age, debility of constitution, chronic lung diseases, bronchitis, and asthma.)
9. What was the ordinary duration of the disease?
   ((1) Acute stage lasting 2 to 5 days; and (2) more chronic stage, 5 to 10 and 14 days.)
10. Were relapses common?
    (Much difference of opinion.)
11. Were persons whose occupations exposed them to the vicissitudes of the weather in the open air more liable to the distemper than those who were confined chiefly to the house?
    (Answers from all parts of the country, with scarcely an exception, were in the negative.)

[52] Thomson, T.: Annals of influenza or epidemic catarrhal fever in Great Britain from 1510–1837. 8°. London, 1852.

12. Are you in possession of any proof of its having been communicated from one person to another?
(Answers uniformly in the negative.)
13. In persons attacked by the epidemic who at the same time labored under pulmonary disease, was the former malady found to be aggravated on the subsidence of the influenza?
(Uniformly "Yes.")
14. Were there any circumstances that appeared to exempt individuals from an attack of the disease, and in particular did the having been attacked during the last similar epidemic of the year 1834 appear to afford any protection?
(The greater number of replies agreed that an attack in former epidemics afforded no protection—no circumstances which appeared to exempt from an attack of the disease.)
15. What were the usual symptoms of the complaint?
(Catarrhal sneezing, nasal discharge, cough, headache, pain, and prolonged prostration.)
16. What unusual symptoms occurred in your practice?
(Meningitis, paralysis, neuralgic pains.)
17. What was your mode of treating the disease?
(Elimination, tonics, counterirritants, confinement to bed, etc.)
18. Did any peculiar atmospheric phenomena precede or accompany this epidemic?
(Answers very general as to temperature, storms, direction of winds, etc.)

Dr. W. T. Vaughan[53] has gone into a rather exhaustive study of the epidemiology of influenza in the American Journal of Hygiene. He names the three following theories as to the origin of influenza:

1. Influenza endemic in some locality, such as Turkestan in Asia, from which place the disease spreads throughout the earth at intervals after having acquired in some way greatly increased virulence.
2. Similar to (1) except more than one endemic focus (Old World and New).
3. The virus of influenza is more or less distributed uniformly throughout the world. As a rule, the virulence does not become so great as to cause a true pandemic, but at rare intervals, usually of decades or thereabouts, the epidemic virus becomes so greatly enhanced, perhaps from passage to new territory and through nonimmune individuals, that it eventually commences on its wild career around the earth.

His deduction as to the behavior of influenza is summed up in the following eight statements:

(1) Occurrence of true pandemics at wide intervals, primarily intervals of several decades.
(2) Indefinite knowledge and conflicting evidence regarding site and manner of origin.
(3) Apparent transmission chiefly or entirely through human intercourse.
(4) Rapid spread over all countries, the rapidity roughly paralleling the speed of human travel.
(5) Rapid evolution of the disease in the communities where outbreaks occur, with nearly equally rapid subsidence after several weeks' duration.
(6) Apparent lack of dependence on differences of wind or weather, seasons, or climate.

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[53] Vaughan, Warren T.: Influenza: An epidemiologic study. Am. Jour. of Hyg., Vol. I, July, 1921.

(7) Generally low mortality in contrast to enormous morbidity. Variation in the incidence of disastrous secondary infections.

(8) Tendency to successive recurrences at short intervals.

Vaughan briefly describes the 1918 epidemic in the same treatise in the following manner:

(1) Wave form.

(2) Broke out with apparent suddenness and showing an undoubted rapidity of evolution.

(3) The epidemic was remarkable in respect to the mortality. The peculiar character of this pandemic was that the type of age distribution which had consistently characterized influenza mortality for many years suddenly and completely changed with the onset of the summer epidemic of 1918. Deaths at 0–15 years of age increased from 7 to 11 per cent (of the epidemic of 1889–1892) to 25 per cent; at 15–35 years of age, from 8 to 10 per cent to 46 per cent; at 35–55 years of age there was little or no change; but deaths at 55–75 years of age and upwards, which formerly provided 60 to 70 per cent of the total registered, contributed in this epidemic only 10 per cent up to 75 per cent and 2 per cent over 75 years of age. In a word, this epidemic presented a sudden and very remarkable change in the behavior of influenza. It destroyed not the very young or the old but the adolescent and the adult. What is the explanation of this complete change of age incidence? The customary explanation is that the older persons in the population may have enjoyed an immunity, owing to attacks in a previous epidemic (in this case, 28 years before) or in intervening prevalence. But the obtainable evidence is to the effect that the degree and extent of such acquired immunity is slight, transient, variable, and incomplete. A second explanatory suggestion attributes the change in age incidence to alterations in the circumstances of the population. Soldiers have been aggregated for war purposes, young men and women in munition works, large sections of adult populations have moved in bulk, owing to trade or transport exigencies, and thus the disease had greater opportunity of fastening upon these aggregated populations under exceptional surroundings. But this epidemic was a pandemic, and all classes came within its ambit; the change of age incidence occurred in nonbelligerent countries not directly affected by the privations of war, and in all parts of the world; lastly, it occured suddenly at the outset (and not as a sequela), differentiating itself clearly from the influenzas of 1917. A third explanation is that the adolescent and adult population were suffering from the debilitating influences of war, from strain, and from exposure. No doubt this factor played a part, but we can not escape the knowledge that the epidemic ravaged populations of the age period who were not subjected to these unfavorable circumstances. A fourth suggestion is that of a more narrowly biological character. It propounds the view that the epidemic was the pathological expression of a new strain of infecting virus, or one to which adolescent and adult tissues were particularly susceptible. This seems to require for its support evidence of importation or of origin of such a virus, and we have few or no facts in that behalf. Moreover, the characters of the disease which proved most fatal and which we must assume would be attributable to such a new or enhanced virus had already manifested themselves sporadically and even epidemically in England, France, and America in the years immediately preceding the pandemic; and, still further, it must not be forgotten that the changed age incidence, in short, was peculiar to the whole emergence of the pandemic, mild or severe, and it was almost universal, under diverse conditions of economic, social, and racial environment.

(4) Its relation to the social condition of the people affected, no class being exempt.

(5) Relation of influenza to other contemporary diseases.

DIFFERENCE BETWEEN PANDEMICS OF 1889 AND 1918.

Much has been written regarding the difference between the pandemics of 1889 and 1918. Vaughan's contribution is that a review of the medical literature between 1889 and 1918 reveals the fact that between 1890 and 1900 the disease in general was more highly prevalent in most localities than at any time during the preceding 30 years, and that at no time during this decade did the annual death rate from influenza in England and Wales fall to anywhere near the figures that prevailed consistently between 1860 and 1889. Between 1900 and 1915, he says, a gradual diminution took place, but not to the extent which existed previous to 1889. There has been a gradual increase since 1915. During the entire period there has been difficulty in distinguishing between the disease and other respiratory contracted infections, particularly coryza and sore throat, tonsillitis, and bronchitis.

Commissioner Abbott,[54] of the Massachusetts State Board of Health, said that in the epidemic of 1889 the ratio of the population of Massachusetts attacked was about 40 per cent. People of all ages suffered, but the ratio of adults was greatest, old people next, and children and infants last. More males were attacked than females. The duration of attack was three to five days. The predominating symptoms were nervous, catarrhal, enteric; but this last was less common than the others. The chief sequelæ were bronchitis and pneumonia.

In a discussion of the differences between the two pandemics of 1889 and 1918, Alfred Stengel [55] says:

> The general type of the pandemic of 1889 was undoubtedly milder than was that of the present outbreak and the number of cases less, but the type of the disease and its complications were not at all dissimilar. In 1889 the symptoms at the onset were general muscular pains, headache, backache, and prostration. There was in the beginning of the epidemic a rather striking absence of catarrhal symptoms than in the earlier stages of the disease, which led the Paris clinicians to regard the disease as dengue. Later cases, however, showed increasing prevalence of a rare type with bronchial and pulmonary sequela, well-marked high fever (102°–104°), and a comparative slow pulse. These last two symptoms were also those observed in the 1918 epidemic.
>
> In 1918 the onset of the disease was much like that in 1889, although nervous symptoms were less marked and catarrhal symptoms more pronounced. Cyanosis was a striking symptom, while cough and catarrhal symptoms were conspicuous from the beginning, differing from 1889. Physical signs were practically identical with those seen in 1889, but developed more promptly and were more conspicuous. The relative infrequency of the pulse noted in

[54] Abbott: Records of Massachusetts State Board of Health, 1890.

[55] Stengel, Alfred: Medical clinics of North America, 1918.

the former epidemic was far less striking than in 1918. Gastrointestinal symptoms were more common in the 1918 epidemic, though cases of the gastrointestinal type were more rare.

The 1918 epidemic was not greatly different from the earlier one as far as nervous symptoms are concerned, though, on the whole, these symptoms seem less marked. In 1918, in the beginning, short cases recovering quickly and severe ones terminating in rapidly fatal pneumonia without complications were conspicuous. Later, the cases were less acute and pleural complications began to become more frequent. Toward the end of the epidemic the hospital wards contained numbers of influenzal and pneumonia residuapleural thickenings, pyena, etc. In all these particulars the 1918 epidemic was not different from those of the past.

At the same time, Jordan,[56] of Chicago, offers these deductions:

The 1918 epidemic is sharply marked off from the influenza of the preceding years by (1) the greater relative mortality at ages 25 to 35, (2) the relatively increased mortality in the white race as compared to the increased mortality in the negro, (3) the higher mortality in white males than in white females, and (4) the relatively increased mortality in colored males as compared with females of the same race.

Although the doctrine of changes and type of disease has sometimes been advanced as an explanation of the difference between the 1918 epidemic and the so-called influenza of the preceding decade, fundamental differences of age, sex, and race mortality in different outbreaks of a specific disease have never been shown to occur and are difficult to explain as epidemic manifestations recurring uniformly at irregular intervals. There is no escape from the conclusion that the so-called influenza of inter-epidemic years is in whole or in part different from the influenza of the great epidemics of 1918 and 1890. A great many of the deaths recorded under the name influenza in the years between epidemics are centainly not due to the same microbic causes as those occurring in epidemic years.

MORTALITY AND MORBIDITY STUDIES.

The mortality and morbidity studies in connection with the epidemic phase of influenza have also been the subject of much investigation and report. Vaughan speaks of the findings of Winslow and Rogers, who studied the relation of the pneumonia death rate of 1901 to 1916 to the influenza death rate of 1918 in 40 large cities of the United States. To quote:

Cities characterized by a higher pneumonia rate in the past are precisely the cities which suffered most severely in the 1918 outbreak.

There is also the same correlation between the total death rates and the influenza death rates. They believe the corollary due to general weakness in population, to tuberculosis, heart disease, etc., or to general economic and social conditions.

Or, finally, it may be that the high rate from tuberculosis and organic disease in 1916 was due to these latter factors, while the high incidence of influenza was due chiefly to proximity to the original focus of infection. None of these explanations is considered entirely satisfactory.

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[56] Jordan, E. O.: Interepidemic influenza. Am. Jour. Hyg., Feb. 28, 1922.

Raymond Pearl,[57] of Johns Hopkins, in studying the mortality rate of 40 cities during the epidemic of 1918, finds a possible correlation between this death rate and the general death rate. Pearl reports that:

In the first study the weekly mortality statistics of the influenza epidemic beginning in the autumn of 1918 have been analyzed in a preliminary way for some 39 large American cities. In the first instance it was shown that there was an extraordinary degree of variation amongst the several cities in this group with respect to the relative degree of explosiveness of the outbreak of epidemic mortality. The first problem confronting the student of the epidemic was the analysis of this variation to find, if possible, primary factors concerned in its causation. Such an analysis, by the method of multiple correlation, appears to demonstrate that an important factor so far found in causing the observed wide variation amongst these 39 American cities in respect to the explosiveness of the outbreak of influenza mortality in the autumn of 1918 was the magnitude of the normal death rates observed in the same communities, particularly those death rates from pulmonary tuberculosis, diseases of the heart and of the kidneys.

Frost[58] conducted studies in cities all over the United States, after which morbidity and mortality studies were made. In this work 10 cities were canvassed in all sections of the United States, including 130,033 persons, 36,365 cases, and 583 deaths. The course of the epidemic differed, being sharply explosive with a six to eight weeks' duration in New London, Baltimore, Little Rock, and San Francisco. The curve was similar but less acute at San Francisco. The epidemic was more protracted at Spartanburg, Augusta, Macon, Louisville, and Des Moines. The morbidity index in all localities was 280 per thousand, but nearly three times more per thousand in San Antonio than in New London. He says:

Considering all localities, the excess of incidence in females was 6 per cent. Considering individual localities, the differences ranged from an excess of 19 per cent to a deficiency of 2 per cent, a lesser incidence among females being shown in only 2 of the 11 localities.

For all localities in males and females of each 5-year age group, the incidence in females was higher in each age period except under 5, 10 to 14, 40 to 44, and 70 to 74.

The excess of incidence in males in these groups is relatively small and is hardly significant in the highest age group where the rates are computed from small figures. The most striking excess of incidence in females occurs between the ages of 25 and 40, the difference between the sexes being relatively slight in age periods above and below these limits. These facts indicate that, in general, females over the age of 15, especially between the ages of 15 and 45, were either more susceptible to infection or more generally and more intimately exposed than males of corresponding age.

The colored were less affected than the whites.

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[57] Pearl, Raymond: Influenza studies. Pub. Health Rep., Aug. 8, 1919.
[58] Frost, W. H.: Statistics of influenza morbidity. Pub. Health Rep., Mar. 12, 1920.

The fatality was higher by 1 per cent of seacoast cities over inland cities.

As to the value of these statistics, they represent so few localities that, taken alone, they represent so little of the country at large. Nevertheless, considered in connection with the far more extensive mortality statistics available elsewhere, they have a definite significance, for even though they do not suffice for the frequency of mortality statistics in the terms of mortality, they at least indicate in a general way some highly important relations between morbidity and mortality, relations which must be borne in mind in applying mortality statistics of epidemics to various important phases of epidemiology.

COMMUNICABILITY AND IDENTITY.

Dr. J. G. Cumming [59] made some exceedingly interesting experiments regarding the effect of the sterilization of mess gear on the incidence of influenza. He believes that transmission of the dangerous groups of pneumonia-producing organisms incident to promiscuous messing in the Army, in public institutions, in public eating places, and in the home can be prevented largely by the disinfection of eating utensils with scalding water. He says:

* * * The universal application of the principle of proper eating-utensil disinfection will reduce enormously the presence of all sputum-borne infection. As is shown in the institutional population, the influenza-case rate was reduced by 66 per cent, and the mortality by 55 per cent, through the use of machine-washed dishes.

Cumming believes that a further reduction in these rates would have occurred had the full efficiency of all mechanical dishwashers been utilized by the use of boiling water.

The whole question of of the epidemiology of influenza is reviewed by a committee appointed by the American Public Health Association. This report,[60] dealing with the 1918 epidemic alone, is very conclusive and is quoted in abstract as follows:

The present epidemic is the result of a disease of extreme communicability. So far as the information available to the committee shows, the disease is limited to human beings.

The microorganism or virus primarily responsible for this disease has not yet been identified. There is, however, no reason whatsoever for doubting that such an agency is responsible for it. Mental conditions may cause a person to believe he has influenza when has not, and may make the patient who has the disease suffer more severely than he otherwise would. No mental state, alone, however, will cause the disease in one who is not infected by the organism or virus that underlies the malady.

While the prevailing disease is generally known as influenza, and while it will be so referred to in this statement, it has not yet been satisfactorily established that it is the identical disease heretofore known by that name, nor has it been definitely established that all preceding outbreaks of disease styled at the time "influenza" have been outbreaks of one and the same malady.

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[59] Cumming, J. G.: Jour. A. M. A., Dec. 6, 1919, vol. 73, p. 1798.

[60] Report on epidemic of influenza, Jour. A. M. A., Dec. 21, 1918, vol. 71, p. 2068.

There is no known laboratory method by which an attack of influenza can be differentiated from an ordinary cold or bronchitis or other inflammation of the mucous membranes of the nose, throat, or pharynx.

There is no known laboratory method by which it can be determined when a person who has suffered from an attack of influenza ceases to be capable of transmitting the disease to others.

Laboratories are necessary agencies for the supervision and ultimate control of the disease. The research laboratory is necessary for the discovery of the causative microorganism or virus and for the discovery of some practicable method for the propagation of a specific vaccine and a curative serum. Clinical laboratories are necessary for the supervision and control of such vaccines and serums as may be used from time to time for the prevention of the disease and for therapeutic purposes and for the information such laboratories can give to health officers and physicians as to such variations in the types of infective microorganisms as occur during the progress of an epidemic.

Deaths resulting from influenza are commonly due to pneumonias resulting from an invasion of the lungs by one or more forms of pneumococci, or by one or more forms of streptococci or by the so-called influenza bacillus or bacillus of Pfeiffer. This invasion is apparently secondary to the initial attack.

Evidence seems conclusive that the infective microorganism or virus of influenza is given off from the nose and mouth of infected persons. It seems equally conclusive that it is taken in through the mouth or nose of the person who contracts the disease, and in no other way, except as a bare possibility through the eyes, by way of the conjunctivæ or tear ducts.

A careful perusal of the above report indicates without question that our knowledge is indeed meager. To repeat one deduction from this committee:

While the prevailing disease is generally known as influenza, and while it will be so referred to in this statement, it has not yet been satisfactorily established that it is the identical disease heretofore known by that name, nor has it been definitely established that all preceding outbreaks of disease styled at the time "influenza" have been outbreaks of one and the same malady.

Emerson [61] cites the uncertain ground for speaking of influenza in epidemiological terms. He emphasizes the doubtful dependability placed on a symptom complex alone, at the same time implying that the Pfeiffer bacillus is the etiologic agent. He says:

In using the word epidemiology when speaking of influenza, one is on uncertain ground, as the primary facts upon which epidemiological studies were based were, and would continue to be, unknown until cases of this disease and deaths from it, as those from other diseases of the respiratory tract, were reported correctly on a basis of morphology or symptom complex. Although in epidemics influenza might attack as many as 40 per cent of a community, the identity of so-called influenza was based on clinical facts rather than on correct or verified etiology. In other words, influenza, an acute and communicable disease, due apparently in all cases to invasion through the upper respiratory tract by the influenza bacillus of Pfeiffer, was not identical with the infectious colds called grippe or influenza by the clinician and certified commonly as a cause of death.

[61] Emerson, Haven: New York Med. Jour., January, 1917, p. 573.

From what is known of the presence of the influenza bacillus in nasal and throat discharges of patients and carriers, and from the bacteriological evidence that the vitality of the organism was lost rapidly if moisture was withdrawn, and that it readily could be recovered in viable state for as long as four hours after discharge from the nose, if suspended in moist droplets, it might properly be inferred that the infection was passed by personal contact, using that term as including all means of conveying the nasal or mouth discharge from person to person by direct or indirect means.

QUARANTINE MEASURES.

During the 1918 epidemic, strong in the belief that the only way to transmit the disease was through direct contact, the Australian Government made influenza a quarantinable disease, since it was at that time raging in all the countries around the island and, to all appearances, was not present there. All vessels with influenza on board and all those coming from New Zealand and South Africa, whether influenza was on board or not, were held to perform seven days period of quarantine for observation. In the case of South African vessels, if the master could furnish evidence that there had been no contact with shore, such vessels were given pratique.

This quarantine was applied in October, 1918, and lasted until August, 1919. During this period there came into Australian ports 149 uninfected vessels with 7,075 passengers and 7,941 crew, while there were 79 infected vessels with 2,795 patients, 40,072 passengers, and 10,456 crew.

In spite of the rigid quarantine, influenza invaded Melbourne on January 9, 1919, and spread rapidly. There was no evidence of any traceable connection between any quarantined vessel and any shore epidemic; there was a period of four weeks between the arrival of the last infected vessel and the first shore case notified. According to the report of the chief quarantine officer:[62]

There is in fact no positive evidence that the influenza in Australia was due to the escape of infection through the quarantine first line of defense. There is on the other hand, both in the nature of the disease and in the history of influenza in Australia during the past 12 months, much evidence in support of the hypothesis that the present epidemic form of influenza is the product of a slow evolution of an influenza already established in Australia in July and August, 1918.

It is reported that the influenza was mild, the death rate being only 33 per 100,000, which would seem to indicate that the virus at that place was old and established and that no new virus was introduced.

EARLY DIFFERENTIATION BETWEEN INFLUENZA AND COMMON COLDS.

In connection with the Australian epidemic, Doctor Hall[63] reports as follows:

Both epidemic influenza and ordinary catarrh are of frequent occurrence in Tasmania. They are often confounded together in the registry. In 1838

[62] Cumpston, J. H. L.: Service Publication No. 18, "Influenza and maritime quarantine in Australia," 1919.

[63] Hall: Epid. Dis. of Tasmania, Vol. II, i, p. 82.

this country suffered in the months of October, November, and December severely from what was commonly called influenza, but which was in fact *catarrh* [b] of asthenic character, frequently merging into acute bronchitis and pneumonia.

Here, again, is another example of such an intimate correlation between common colds and influenza that, in this instance, they are indistinguishable in epidemic form. In this connection the following is again quoted from a paper read before the Royal College of Physicians in London in 1785 by Dr. W. Heberden:

> In the very beginning of June, if not sooner, a few persons in London were affected with several symptoms of a cold, which, of their own accord, they in two or three days observed to differ from a common cold, and to resemble the epidemical one of the year 1762, on account of its being attended with a greater languor, feverishness, and loss of appetite than what the same degree of such a complaint usually brings on. About the middle of June the same disorder began to be much more common in London and was manifestly epidemical. It was at its height about the last week in June and the beginning of July, and before the end of July had entirely ceased.

RECENT STUDIES ON THE COMMON COLD.

Coincident with influenza studies made since the last epidemic, there has been a revival of interest in the study of the epidemiology of the common cold. Some of the investigations made and some of the material gathered may be summarized in the following reports:

Dr. Eugene C. Howe [64] took a census of colds in a class of 367 freshmen at Wellesley, from October, 1919, to April, 1920. The following figures are quoted:

Number and distribution of colds.

Distribution	26	84	101	91	40	18	3	2	1
Number of colds	0	1	2	3	4	5	6	7	8

Total number of colds, 849.
Total number who had colds, 341.

Duration.

	Per cent.
4 days or less	29
5 days to 7 days, inclusive	35
8 days to 14 days, inclusive	25
15 days or more	11

Type of colds.

	Per cent.
Head	65
Throat	13.5
Head and throat	9.5
Chest	12

Effect on efficiency.

	Per cent.
None	33
Very slight	22
Moderate	18
Considerable	27

[b] Italics are the writers.

[64] Howe, Eugene C.: Census of colds in a class of 367 college freshmen, October, 1919, to April, 1920. Am. Jour. of Pub. Health, May, 1924, p. 435.

The general facts stand out clearly, even though roughly, that (1) only 26 out of 341 persons, or between 7 and 8 per cent, were free of colds; (2) many colds were of considerable duration; (3) head colds predominated; (4) almost half of the individuals concerned reported either moderate or considerable decrease in efficiency, while almost a third reported a considerable decrease. From such a group one can expect understatement rather than exaggeration of inconvenience caused by the "common cold."

Dr. D. F. Smiley [65] conducted investigations among the students of Cornell University, month by month, for four years and deduced some information which, while negative, is of some value:

A monthly record of the acute infections of the throat and respiratory system has been kept for the last four years at the Cornell University medical adviser's office. This record has shown, year after year, a gradual rise to a maximum number of cases in January, February, or March, and a gradual fall as summer approached. * * * Table I shows that the year 1919–20 was apparently an epidemic year for these diseases, and that this was followed by a year with few such infections. The year 1921–22 shows a slightly increasing prevalence, and 1922–23 shows the infections again assuming epidemic proportions.

TABLE I.—*Incidence of acute infections of the throat and respiratory system in male students of Cornell University, month by month, for the last four years.*

Year	October.	November.	December.	January.	February.	March.	April	May.	June.
1919–20	291	194	249	572	275	312	256	216	27
1920–21	197	188	195	184	177	283	107	116	28
1921–22	345	213	281	355	398	397	209	191	20
1922–23	158	215	378	314	473	654	382	228	92

TABLE II.—*Relative importance of acute infections of throat and respiratory system.*

Year.	Total consultations.	Consultations for acute respiratory or throat infections.	
		Number.	Per cent.
1919–20	13,619	2,392	17.4
1920–21	13,280	1,475	11
1921–22	16,655	2,409	14.4
1922–23	16,832	2,894	17.2

TABLE III.—*Distribution of colds according to frequency.*

	Group 1, none or one.	Group 2, two or three.	Group 3, four or more.
Men ..... per cent	15.4	58.2	26.2
Women ..... do	18.8	61.3	19.5
Average	17	60	23

[65] Smiley, D. F.: A study of the acute infections of the throat and respiratory system. Jour. A. M. A., Feb. 16, 1924.

Such results, however, seem to point the way to a few cautious conclusions:

1. Tobacco, dust, gas, mouth breathing, sleep, drafts, constipation, perspiration, bathing, and footwear are apparently not major factors in determining resistance to respiratory infections in this particular group.

2. Exercise appears as a liability rather than asset in this group (probably because of improper care of the body in the stage of fatigue following the usual violent sport).

3. The use of woolen underwear is apparently no panacea for the prevention of "colds"; in fact, it seems almost safe to infer that the use of light underwear is preferable under conditions obtaining at Ithaca.

4. Heredity may be a factor in determining resistance through carrying on to the next generation a "catarrhal diathesis" or the opposite.

5. Since removal of nasal obstructions and diseased tonsils in more than half of the "four or more" group has not resulted in the reduction of the frequent "colds," it seems fair to conclude that nasal obstructions and diseased tonsils are not major factors in the majority of persons suffering with frequent "colds."

6. Of all the factors listed, only one (that of underclothing) showed a difference of more than 15 per cent in the two groups, and that *only 19 per cent.* It might be concluded, therefore, that, though underwear is of some importance, no major factor has been dealt with in the whole questionnaire.

What the major factors in susceptibility to colds are, is, therefore, as far as the work at Cornell University is concerned, still a matter of conjecture. There is an inclination toward the supposition that there is a specific lack of immunity in certain persons to the organism or organisms that cause "colds," but until the etiology of these infections is definitely settled a specific prophylactic can not be looked for.

As a test of the prophylactic value of the present respiratory vaccines, a small number of the "four or more" group was inoculated once a month with one of the much-used types of respiratory vaccines on the market, but no reduction in frequency of "colds" was noted in the majority of cases. Investigations along this line seem to offer some hope of success, however, and the therapeutic inoculation of a large number of patients while they are suffering from "colds" will probably be attempted the coming year. The objective will be to prevent severity, prolongation, and complication (so often caused by the known secondary invaders). On theoretical grounds, at least, such an objective is not impossible of attainment if the respiratory vaccines are considered capable of combating the known secondary invaders; and if it is considered that the unknown virus itself (which we may assume is the true etiologic factor) is capable of running only a mild course.

Jordan, Norton, and Sharp [66] in 1923 conducted similar experiments in groups of people in Chicago, Los Angeles, and Galveston. They sent questionnaires to groups of students at the universities in these three cities and tabulated the results. Their report may be briefly summarized:

1. The common cold generally starts in the nose. About one-third of these colds extend to the chest.

2. The sequence of the local symptoms in colds is not uniform.

3. There is no definite correlation between types, duration, severity, and frequency of colds, except that infrequent colds tend to run a milder course.

[66] Jordan, E. O., Norton, J. F., and Sharp, W. B.: The common cold. The Jour. of Inf. Dis., November, 1923.

4. In our California and Galveston groups colds, while of about the same yearly frequency as in the Chicago group, tended to be concentrated into a shorter period, were of somewhat less severity, and of somewhat shorter duration. In general, however, the differences in the three groups were less than might be expected on the basis of climatic conditions alone.

5. Of the persons from whom data were gathered, 64 per cent believed that their colds were induced by some strain on the heat-regulating mechanisms of the body.

6. Possible contact with others having colds was stated to have preceded their own colds by 22 per cent of persons questioned.

7. "Resistance building" practices apparently had little effect on the frequency of colds.

8. Our data do not show that nose or throat operations result in a marked reduction of the frequency of colds.

9. Among the bacteria cultivable on blood-agar plates, no one bacterium or group of bacteria has been found to predominate in the upper respiratory tract during a cold.

10. Whether or not a cold is the result of a specific infectious process is unknown. It is clear, however, that outside influences, particularly those involving chilling of the body, may serve to induce a cold, even if these influences can not be regarded as the most important etiologic factors.

The epidemiology of colds in infants was the subject of a study by Winholt and Jordan.[67] Their summary is interesting:

1. Records of 500 babies with, and 500 without, colds showed that the occurrence of colds in these infants was accompanied by a relatively high proportion of colds in the respective families.

2. The existence of a cold in the mother of a baby was accompanied by a cold in the baby in a disproportionately larger number of cases.

3. The general resistance to such exposure seems, however, quite high. Exposure to mothers' colds has occurred in nearly half as many cases of babies without colds and those with colds.

4. The findings suggest a relatively widely disseminated virus of low infectivity, since babies with colds and babies without colds had been equally exposed to the colds of the father alone. Apparently the average contact exposure necessary for infection exceeds that ordinarily obtaining between father and baby.

5. The incubation period of colds is probably very short. Nearly all of the babies' colds which were contracted after exposure within the families showed symptoms before the preceding patient's cold had disappeared.

6. Coincident ailments, indicating lowered resistance, especially those of deranged metabolism, were much more common in babies with colds than in those without colds.

The age of the babies studied was from birth to 2 years.

The Metropolitan Life Insurance Co. reports one year of common colds and associated infections among its employees and indicates the enormous economic loss which results. In this report it is stated:

The amount of absenteeism in large business and industrial establishments due to minor illnesses is seldom appreciated until the facts are thoroughly reviewed. The common colds are among the chief sources of lost time. In a group of about 6,700 clerical employees of the Metropolitan Life Insurance Co.

[67] Winholt, W. F., and Jordan, E. O.: Epidemiology of colds in infants. Jour. A. M. A., July 28, 1923.

at the home office, during the 52 weeks ending July 28, 1923, 2,824 colds which involved disability for work were reported to the medical division, which cares for the health of the clerical staff. These disabling affections occurred at a rate of 420.7 per 1,000 employees for the year. The average days of disability for this illness per person on the pay roll for the year was 0.9, and the average days per case were 2.2. In all, there were 6,233 days lost in the year from these conditions, which included head colds or coryza, acute bronchitis, and tracheitis. Other associated conditions were excluded because of the impossibility of determining in how many cases they were associated with common colds.

A study of these reports and investigations made by persons of equal reputation from various parts of the world and during widely separated intervals of time can not help but impress one with the idea that our present knowledge of the epidemiology of influenza, and the etiology as well, is veiled in a mass of personal opinions of wide variation and little agreement—at least, not enough agreement to warrant any definite statements which may be accepted as throwing any light on this matter. Although we speak of influenza and the common cold (epidemic coryzas or catarrh, which may be taken to mean one and the same thing) as separate entities, it seems to be impossible for investigators who study the epidemiology of both conditions to separate conclusively influenza from the minor respiratory disorders, of which the common cold is a notorious example.

Immunity.

IMMUNITY CONFERRED BY AN ATTACK.

The question of whether or not one attack of influenza confers immunity against subsequent attacks is only another feature of this disease which has brought forth much disagreement. It may be stated, however, that it seems to be the general consensus of opinion that one attack of the disease does confer a slight immunity. The following observations from previous studies emphasizes the fact that whatever immunity exists is, in the main, slight.

A history of relations between the epidemics of April, 1918, and October, 1918, at Camp Hattiesburg, Miss., is very interesting and is quoted from Dr. W. T. Vaughan [68] as follows:

An epidemic of mild influenza struck the camp at Hattiesburg, Miss., in April, 1918. Within about 10 days there were 2,000 cases among 26,000 men. This division remained in this country without change of station from April until the fall of 1918. During the summer, this camp received 20,000 recruits. In October, 1918, the virulent type of influenza struck this camp. It confined itself exclusively, almost, to the recruits of the summer and scarcely touched the men who had lived through the epidemic of April. Not only the 2,000 who had had the disease in April escaped, but the 24,000 who apparently were not

[68] Vaughan, Warren T.: Abstract in Jour. A. M. A., Sept. 20, 1919, p. 886.

affected escaped the fall epidemic. It would appear from this that the mild influenza of April gave a marked degree of immunity against the virulent form in October.

Another observation points the same way. Looking over the statistics of the fall epidemic in cities of the United States, we find that certain cities had a low death rate, as Atlanta, Ga., Kansas City, Mo., Detroit, Mich., and Columbus, Ohio. The spring records show that in March and April, 1918, there was in these cities an unusually high death rate from pneumonia, and undoubtedly there was also at that time a relatively mild epidemic of influenza. This would account possibly for the relatively low death rate in the fall of 1918. Though no claim is made that this and other instances prove that the mild and virulent forms of influenza are manifestations of the same disease, the evidence seems to point that way.

Further on the subject Vaughan says:

Opinions of all observers who have studied in detail the question of immunity from influenza are remarkably in accord. The conclusions reached by Parkes in 1876 are valid to-day and form an excellent abstract of our present knowledge, as excellent as any produced since his time. There is some discrepancy of evidence, but, on the whole, it seems clear that, while persons seldom have a second attack in the same epidemic (though even this may occur), an attack in the one epidemic does not protect against a subsequent attack. Indeed it has been supposed rather to render the body more liable.

At a meeting of the Chicago Society of Internal Medicine held on February 23, 1920, the following discussions were evidently indicative of the doubt in the minds of some as to whether or not immunity is conferred:

Dr. Joseph A. Capps: "Does one attack of influenza confer immunity? I have seen several cases recently which lead me to believe that it does not. One patient had leukopenia, respiratory symptoms, great prostration, and other symptoms associated with influenza, and recovered. This patient went to Florida and again developed a fresh attack. Another patient, after having recovered from the primary attack of influenza, went to California and, several weeks after the first attack, had a second one. I presume one can say this was a recurrence or perhaps a relapse, such as we had in typhoid fever cases."

Dr. E. K. Kerr: "In connection with immunity, we were struck by the epidemic September 20, 1918, which ran for about six weeks. During that time we had about 6,000 cases of influenza in our camp of 35,000 or 40,000 men. About two days before the armistice a troop movement started from the rural districts in Minnesota. The men were collected in Minneapolis and sent to Chattanooga. The men who were attacked with influenza were dropped off the train at different places. They had the same type of influenza that was prevailing in the camps. While the original epidemic was on the ward attendants, nurses, and physicians were coming down with the disease in the same proportion as the men in the camps. While the batch of men came in from Minnesota there was practically no spread of the disease."

Dr. Bernard Fantus: "Last year I had quite a number of patients who, two or three months after the primary attack, developed another attack. In the meantime they had been entirely well. I have had a few patients who have developed a third attack about two months after the second attack. I think all practitioners have noticed that in this year's epidemic many indi-

viduals were taken sick who were sick with influenza last year. Again, some patients who had severe attacks last year have had mild cases this year, and vice versa."

Jordan and Sharp,[69] in a report on "Immunity in influenza," give the following:

Influenza epidemics broke out about January 12, 1920, at the Great Lakes Naval Station, containing perhaps about 5,500 or 6,000 men, and in Camp Grant, containing 4,400 men. In each post a census was taken in order to divide the men into groups of those attacked and those not attacked in the 1918–19 epidemic and to determine the number in each group attacked in recent epidemics. The results indicated that no marked immunity from influenza exists 12 to 15 months after a previous attack.

These observations by Jordan and Sharp are not altogether concurred in by Armstrong and Hopkins,[70] who made a survey of the 1920 epidemic on Kelly's Island, Ohio. Their conclusion was that a relative immunity seems to be apparent 15 months after the 1918 epidemic.

Frost[71] states:

Concerning the important question of the immunity conferred by an attack of influenza, the evidence is not conclusive, chiefly because of the uncertain differentiation between influenza and other infections. Parsons, from his study of the last epidemic, inclines to the view that an attack of influenza in the earlier years of the epidemic conferred a considerable but not absolute immunity in the later outbreaks.

In an editorial in the Journal of the American Medical Association for October 4, 1919, it was stated that while opinion as to the degree of immunity conferred by one attack of influenza is not unanimous, there are many facts that appear to support the view that one attack does confer immunity to the disease.

THE USE OF CERTAIN GASES IN RESPIRATORY DISEASES.

It has been observed that fumes from certain gases confer a relative amount of immunity against influenza. The Journal of the American Medical Association for May 24, 1919, says:

The information given by Shufflebotham with regard to influenza among poison-gas workers has been collected from 20 different sources, in different parts of the country. It all points in the same direction—that, with the exception of phosgene gas, workers engaged in the production of other gases have enjoyed a very high degree of immunity from influenza infection. On the other hand, phosgene workers are peculiarly susceptible to influenza; and the disease, when contracted, assumes a serious course.

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[69] Jordan, E. O., and Sharp, W. B.: Immunity in influenza. Jour. Inf. Dis., May, 1920, p. 453.

[70] Armstrong, Charles, and Hopkins, Ross: An epidemiological study of the 1920 epidemic of influenza in an isolated rural community. Pub. Health Rep., vol. 36, No. 29, July 22, 1921, pp. 1671–1702. (Reprint No. 678.)

[71] Frost, W. H.: Jour. A. M. A., Aug. 2, 1919, p. 318.

Two Army investigators, Vedder and Sawyer,[72] have taken advantage of these observations in the preparation of a mild chlorine gas for inhalation as a curative for colds and influenza. Their conclusions are as follows:

Inhalation of chlorine of a concentration of 0.015 mg. per liter for one or more hours have a distinctly curative value in common colds, influenza, whooping cough, and other respiratory diseases in which the infecting organisms are located on the surface of the mucous membranes of the respiratory passages.

Dr. Alexander Gregor[73] reports, in the British Medical Journal, the effects of subjecting volunteers to dilute fumes of sulphur dioxide (SO_2) and nitrogen peroxide (NO_2). He finds that swabs from the noses and throats of individuals who have been subjected to the gaseous fumes at various durations leave but little doubt that the fumes have a marked effect in inhibiting postnasal microbial growth in persons exposed to them. He continues:

In all workers except 3 the growth was diminished, in no less than 16 a few colonies were just visible, and 4 plates were actually sterile. Taken as a whole, 74 per cent of the workers had their nasal passages really disinfected.

By workers he means the employees of the shops where the experiments were carried on.

In regard to chlorine gas, he says:

Plates of swabs from two experimenters exposed showed no diminution in growth; and, as the effects of the gas on them were so disagreeable, no further trials were made in this direction. Twenty-four inoculated plates which had been incubated for 24 hours and showed varying growths of the organism were placed in an air-tight box. A massive dose of chlorine gas of a strength of between 1 in 1,000 and 1 in 2,000 was introduced to see if further growth could be inhibited. The box was left at room temperature for 24 hours. On opening the box at the end of this time a distinct odor of chlorine was perceptible, but, notwithstanding this and the massive dose given, there was a distinct increase of growth on the plates.

These studies are still in process and it is yet too early to form any definite conclusions, although the effect of chlorine gas on influenza has been known for some time.

The New York City Department of Health, in its Weekly Bulletin of September 13, 1924, comments on an editorial in one of the leading New York papers regarding the use of chlorine gas as a cure for pertussis. The New York City Department of Health offers the following:

Unfortunately, the observations of the chief medical officers of the department who have been studying the value of chlorine gas in respiratory diseases, have failed, thus far at least, to substantiate the reports of benefits from the

[72] Vedder, Edward B., and Sawyer, Harold P.: Chlorine as a therapeutic agent in certain respiratory diseases. Jour. A. M. A., Mar. 8, 1924.

[73] Gregor, Alexander: The scope of certain gaseous disinfectants in the prophylaxis of influenza. Brit. Med. Jour., Vol. II, 1919.

use of this gas. Should the department, in the course of further researches, find reason to change its present opinion, the members of the medical profession will be promptly informed.

The Journal of the American Medical Association, in its issue of March 22, 1924, comments as follows on the work of Vedder and Sawyer:

Although it may not be the most formidable of the diseases that attack man, the common cold is at least one of the most annoying, and it always brings with it potentialities of a more menacing character. A popular writer has remarked that colds do not "run into" consumption, but they bear much the same relation to it that good intentions are said to do to the infernal regions. They release the lid of a perfect Pandora's box of distempers. A cold, therefore, is no longer a joke. There is to-day little doubt that many of the types of colds, if not all of them, have an infectious etiology. This does not mean that microbial agencies, whether filtrable or nonfiltrable viruses, are present in the affected mucous membranes only when the inflammatory actions give signs of them. The etiologic factors may be dormant until an opportunity arises in the form of altered biologic conditions in the tissues that they infest. In any event, local infection is the keynote of the "cold." Quite naturally, therefore, the hope of being able to disinfect the invaded membranes has long aroused the enthusiasm of the therapeutist who deals with these disturbed structures. Usually he has attempted to steer between the danger of damaging the mucous membranes as well as destroying the microbes by the use of vigorous antiseptics and the futility of procedures too mild to accomplish any germicidal result. Among the products that once awakened enthusiasm, formaldehyde represents an instance of the unduly damaging sort, whereas most of the vaunted mouth lotions belong in the other category. Furthermore, their possible period of action is confined to a very brief period. Local nasolaryngolic treatment is usually in essence merely a sort of local cleansing. It may diminish, though it by no means eradicates, the trouble makers. There is a note of interest, however, in the possibilities of the use of chlorine gas, as outlined by Vedder and Sawyer in a recent issue of The Journal. The observations at the Edgewood Arsenal seem to represent the most carefully controlled tests thus far recorded. According to the Army physicians, inhalations of chlorine of a concentration of 0.015 mg. per liter, for one or more hours, have a distinctly curative value in common colds, influenza, whooping cough, and other respiratory diseases in which the infecting organisms are located in the surface of the mucous membranes of the respiratory passages. There is a background of bacteriologic sense to the scheme. A thousand cases are not, however, many in which to test the effect of treatment of self-limiting diseases. Further developments will be awaited with interest.

VACCINATION.

There is much diversity of opinion regarding the effect of vaccination as an immunizing agent against influenza. Due to the multiplicity of organisms associated in the noses and throats of influenza patients, and the fact that the bacterial flora changes from day to day, also due to the fact that stock vaccines are, of necessity, shotgun in character, it is obvious that there is only a chance that the vaccine

in question will be specific for the organism causing the disease. It must also be taken into consideration that as yet the cause of influenza is not known; and until that fact is definitely established it is impossible to inaugurate a preventive or a curative vaccine. A report of experiments in which various forms of influenza vaccines have been put to the test indicates that, in the main, the percentage of seizures among the vaccinated is as large as that among the unvaccinated.

Jordan and Sharp[74] experimented with approximately 6,000 people at the Great Lakes Naval Training Station. They report that influenza attacks among 2,873 vaccinated persons numbered 118, or 4.1 per cent, while the influenza attacks among 3,193 unvaccinated numbered 152, of 48 per cent. Pneumonia attacked 7 among the vaccinated and 12 among the unvaccinated. The vaccine used for the first dose: *Streptococcus hemolyticus*, 500 M; *Streptococcus viridans*, 500 M; pneumococcus, type I, 1,000 M; pneumococcus, type II, 1,000 M; pneumococcus, type III, 500 M. For the second and third doses the number of each organism was doubled.

Similar results were obtained by McCoy and Murray,[75] of the Public Health Service, in their vaccinations among a group of patients at a State hospital for the insane. Three hundred and ninety people were vaccinated against influenza and the same number remained unvaccinated. There were 119 cases of influenza among the vaccinated, or 30 per cent, while 103 cases developed among the unvaccinated, representing 26 per cent. It will be observed that the number of infections among the unvaccinated was even less than that among the vaccinated. The vaccine used was mixed influenza, four types, pneumonia, *Streptococcus haemolyticus*, and *Staphlococcus pyogenes aureus*.

Maj. H. J. Nichols,[76] of the Army, reports work done by Maj. M. W. Hall at Fort Myer, Va., in vaccination by pneumosintes. These results indicate a very slight protection among the vaccinated (3 per cent). His report is as follows:

> Each winter since the war, with its problem of acute respiratory diseases, active efforts have been made at the Army Medical School to test the value of vaccination against one or more of these diseases. In 1919–20 and in 1920–21 a polyvalent pneumococcus vaccine, Types I, II, and III, was manufactured and issued for trial in selected groups of soldiers, and in 1922–23 a mixed vaccine of pneumococci, streptococci, and influenza bacilli was made and tested. The results of this work need not be discussed at this time, except to say that, with the possible exception of pneumonia due to fixed types of the pneumococcus, no radical progress has been made in the solution of the problem of the control of respiratory diseases by vaccination.

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[74] Jordan, E. O.: Jour. Inf. Dis., April, 1921, 28; 356.

[75] McCoy, George W., and Murray, V. B.: Failure of bacterial vaccination as a prophylactic against influenza. Jour. A. M. A., Dec. 14, 1918, p. 1997.

[76] Nichols, H. J.: Report on vaccination against influenza in the Army with *B. pneumosintes*, 1922–23. Army Med. Bull., Oct. 15, 1923.

For 1922–23, as a result of the promising work on *B. pneumosintes* (Olitsky and Gates), it was decided, if possible, to test the effects of vaccination with *B. pneumosintes* against influenza. Lieut. Col. C. F. Craig, director of laboratories at the school, consulted with Dr. Simon Flexner, director of the Rockefeller Institute, and a cooperative study was decided on. Doctor Olitsky furnished the vaccine and made a preliminary trial for dosage, reactions, and immune bodies on volunteers at the Army Medical School in the fall of 1922. A report of the work was made in the Journal of Experimental Medicine for April, 1923.

The principal experiment was made at Fort Myer, Va., where previous work of this kind had been done. It was under charge of Maj. M. W. Hall, of the Medical Corps. The conditions were favorable, as a definite epidemic of influenza occurred and there was a control group. The results indicate that a slight protection was afforded by the vaccine. The following figures are the most significant of the whole experiment:

	Control.	Vaccinated.
Age group 20–24	183	202
Cases of influenza	31	28
Percentage of cases	16.8	13.8

The difference was 3 per cent, or there was one-fifth to one-sixth less disease among the vaccinated.

Major Hall concludes:

"The results shown seem to indicate further experiment with larger doses of the vaccine.

Results of experiments at Governors Island, N. Y.

	Number of cases.		Percentage of cases.	
	Controls.	Vaccinated.	Controls.	Vaccinated.
Total population	188	175		
Influenza	2	5	1.1	2.6
Other acute respiratory diseases	8	4	4.5	2.1
Total	10	9	5.6	4.7
Tonsilitis	6	10	3.4	5.3
Total	16	19	9.0	10.0

Conclusions.

The general conclusion is that the results are not decisive, as there were not sufficient cases; but several cases of influenza did occur among the vaccinated, and this evidence, with that at Fort Myer, leads to the final conclusion that, with the doses used, vaccination with *B. pneumosintes* did not produce any clear-cut protection against influenza.

In view of our imperfect knowledge of the new group of organisms of which *B. pneumosintes* is a member, it is premature to draw any final conclusion from this vaccination experiment as to the etiology of influenza. The persistent work of the investigators at the Rockefeller Institute has revealed a new group of organisms which can be handled only with laborious technique. The key to the influenza problem very probably lies in this group, but further work is necessary, and at the proper time further cooperative work should be undertaken by the Army.

Lloyd, of the Public Health Service; Ely and Hitchcock, of the Navy; and Nickson,[a] of the Naval Reserve Force, apparently accomplished some interesting work at Puget Sound with vaccines. They prepared a vaccine from organisms which they tentatively though not definitely classed as hemolytic strepticocci persistently found in blood cultures of patients ill with what was diagnosed as influenza. The strains used were fatal to rabbits in 18–72 hours. The Pfeiffer bacillus would have been used in the vaccine if it had been found in the blood.

They report that out of 4,212 men who were vaccinated and who contracted the disease, not one died. Of 9,486 unvaccinated, 96 died. The number of cases among the vaccinated was 144 and among the unvaccinated was 1,359. In their conclusions they say:

> We believe that the use of killed cultures as described prevented the development of the disease in many of our personnel and modified its course favorably in others. We at first used a single strain, but later mixed two or more strains. We do not know that the latter is advantageous.

As in the case of influenza, there seems to be a similar uncertainty regarding the value of vaccination as a preventive of common colds, while the immunity (if any does exist for the common cold) is indeed extremely slight.

Bacteriological Studies.

PFEIFFER BACILLUS.

It has been only since the epidemic of 1918–19 that much interesting work has been done in a bacteriological way to better establish just what rôle is played by the Pfeiffer bacillus in the causation of the disease. Prior to this epidemic the Pfeiffer bacillus was accepted generally as the etiologic agent in influenza, but at the present time this bacillus does not enjoy the same assured position as the definite factor in the etiologic rôle. It is possible to mention only some of the more important experiments carried on with the Pfeiffer bacillus.

To begin with, it has been definitely established that this organism is distinctly pathogenic to certain animals. To quote the conclusions of Albert and Kelman:[77]

> The Pfeiffer influenza bacillus is distinctly pathogenic to mice, guinea pigs, and rabbits. This quality is apparently limited to certain cultures or strains of this microorganism.

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[a] Ely, C. F., Lloyd, B. F., Hitchcock, C. D., and Nickson, D. H.: Influenza as seen at the Puget Sound Navy Yard. The Journal of the American Medical Association, Vol. LXXII, 1919, p. 24.

[77] Albert, Henry, and Kelman, S. R.: The pathogenicity of *Bacillus influenzæ* for laboratory animals. Jour. of Inf. Dis., 1919, Vol. XXV.

The guinea pig is more uniformly susceptible to the influenza bacillus than rabbits and mice, although not so susceptible as some rabbits. Rabbits show a greater variation in individual susceptibility.

Young (half-grown) animals are more susceptible than larger ones.

Intravenous and intraperitoneal injections are slightly more rapidly fatal than subcutaneous injections.

Two cubic centimeters of a 24-hour hemoglobin broth culture of a virulent organish is fatal to about 90 per cent of white mice. Five cubic cetimeters of such a culture is fatal to about 50 per cent of rabbits and 70 per cent of guinea pigs.

Death of animals occurs in from 1½ hours to 30 days after injection. It is probable that deaths occurring after the fourth or fifth days may be caused by secondary invading organisms rather than by the Pfeiffer bacillus.

The chief acute symptoms are listlessness, muscular weakness, rapid and labored breathing, elevation of temperature, and convulsions. The chief chronic symptoms are loss of weight and muscular weakness.

The virulence of the organism varies with cultures from different sources.

The injection of influenza bacilli favors the invasion of tissue by other bacteria. Likewise, the introduction of other bacteria favors the proliferation in the body and the invasion of tissues by the influenza bacillus.

Influenza bacilli are, as a rule, apparently rapidly destroyed soon after introduction into the body. Following injection into the peritoneal cavity they may appear in the blood. This appears to be dependent on either the virulence of the microorganism or a condition of lowered resistance on the part of the body.

The influenza bacillus produces a toxin which is fatal to mice, guinea pigs, and rabbits almost as rapidly as are broth cultures of equal dosage. This toxin is produced very rapidly and can be obtained by filtering broth cultures. It is not possible to state definitely whether it is an endotoxin or an extracellular one.

Although the symptoms of intoxication as seen in lower animals following the injections of the Pfeiffer bacillus are suggestive of the profound intoxication seen in connection with many cases of the epidemic disease influenza in the human being, these experiments do not furnish any proof that the Pfeiffer bacillus has any specific etiologic relationship to that disease. On the other hand, they suggest that a possible etiologic relationship can not be ignored.

Paul Hudson [78] reports the following work with white mice:

Pfeiffer's bacillus when injected intraperitoneally in pure culture was found to be pathogenic for white mice, irrespective of the source, and was readily recovered from the heart blood by cultivation on chocolate-agar medium. Strains isolated during influenza epidemics at military camps were more pathogenic for white mice than strains from other sources. The invasiveness of Pfeiffer's bacillus and streptococcus viridans seemed to have been increased by injections in mixed cultures; the baccillus by injection with pneumococcus and the coccus by injection with Pfeiffer's bacillus. Pfeiffer's bacillus was not found to be appreciably increased in virulence by passage three of four times through white mice.

Sublethal doses 1¼ to $\frac{1}{16}$ slant of strains used of Pfeiffer's bacillus conferred immunity to white mice against lethal (½ slant) and twice lethal (1 slant) dose as of heterologous as well as homalogous strains. This immunity lasted at least eight weeks.

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[78] Hudson, N. Paul: Influenza studies. Jour. Inf. Dis., 1922, vol. 30, p. 425.

Julia T. Parker,[79] in her experiments with rabbits, offers the following:

1. *Bacillus influenzæ* produces a filtrable poison which is lethal to rabbits when given intravenously.

2. The poison is only partly destroyed when heated to 55° C. for one-half hour. When heated to 75° C. for one-half hour or boiled for five minutes, over two-thirds of its toxicity has been lost.

3. Rabbits can be immunized to at least four or five minimal lethal doses of the poison.

4. One-quarter to one cubic centimeter of the immune serum can neutralize *in vitro* one or two lethal doses of the poison.

5. Five to ten cubic centimeters of the immune serum, when given intravenously 15 minutes before or 15 minutes after the injection of one or two lethal doses of the poison, will usually save the rabbit.

6. Five to eight cubic centimeters of immune serum, when mixed *in vitro* with at least three minimal lethal doses of the poison, will save about 50 per cent of the rabbits. Influenza bacteria extracts, fresh or autolyzed, are poisonous to rabbits in relatively large amounts. The symptoms are the same as with a sublethal dose of the broth filtrate.

7. The Berkfeld filtrate of the bacterial extracts is nearly as toxic as the extracts themselves. Boiling this filtrate does not destroy its toxicity.

8. The immune serum has no effect *in vitro* even in large amounts in detoxicating the bacterial extracts.

9. Antiserums produced by immunizing with vaccine of *B. influenzæ* do not neutralize *in vitro* a lethal dose of the broth poison.

10. While the evidence is by no means conclusive, it seems probable that the poison of *B. influenzæ* contains two poisons—the first, the more important one, a true soluble toxin, filtrable, thermolabile, against which antitoxins can be produced; the second, present also in the vaccine of *B. influenzæ*, also filtrable, but differing from the first poison in its thermostability, and in the fact that it is not detoxicated by the antitoxin.

Huntoon and Hannum [80] have discussed the rôle of the bacillus of Pfeiffer in clinical influenza in this manner:

An examination of the experimental evidence of the preceding pages would appear to have established the following facts:

1. That *B. influenzæ* is capable of producing a toxic substance.

2. That this substance when introduced into the circulation produces congestion of the respiratory tract with hemorrhages into the alveoli.

3. That certain conditions of symbiotic growth intensify the liberation of the toxin.

4. That as an effect of the action of the poison the lungs show a predisposition to invasion by various organisms with the production of secondary lesions.

5. That live bacilli introduced at a remote point probably affect the lungs through the action of a liberated toxin.

6. That there is nothing in the serological evidence to preclude the consideration of this organism as an important factor in the causation of clinical influenza.

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[79] Parker, Julia T.: The poisons of the influenza bacillus. Jour. of Immunology, Vol. IV, 1919.

[80] Huntoon, F. M., and Hannum, S.: The rôle of *Bacillus influenzæ* in clinical influenza. Jour. of Immunology, Vol. IV, 1919.

It may be mentioned with respect to the broth emulsion of *B. influenzæ* that when streptococcus filtrate alone is added or when pneumococcus is grown in symbiosis with it the bacilli do not disintegrate but retain both their morphology and staining characteristics, whereas in the lot grown in symbiosis with the streptococcus there remain only a few organisms that could be recognized as *B. influenzæ*, the remainder being represented by shadow forms and detritus.

The observations of these investigators on symbiosis are interesting, and it seems logical to consider them gravely in view of the fact that (1) the bacterial flora of the nose and throat changes from time to time and (2) the influenza bacillus, as will be discussed later, seems to be present in some cases of influenza and absent in others—present in healthy mucous membranes and absent in others. These factors indicate that there is a possibility of the growth of some other organism influencing the growth of the influenza bacillus.

C. Roos [81] reports, in the Journal of Immunology, that in a series of experiments in 1916 he was able to confirm the observations of Jacobson in regard to the symbiosis of *B. influenzæ* with streptococci by injecting freshly isolated strains of *B. influenzæ* into mice alone and in symbiosis with a virulent streptococci, either dead or alive. He found that the symbiosis of these organisms increased the virulence of *B. influenzæ* about tenfold.

The presence of the influenza bacillus on healthy mucous membranes as well as on diseased membranes has also been the subject of much investigation and clinical research. The fate of this bacillus introduced into the upper air passages has been the subject of a study by Bloomfield,[82] of Johns Hopkins, who summarizes as follows:

1. Three strains of influenza bacilli introduced in large amounts into the normal upper air passages disappeared very rapidly within one to two days. In no case was a carrier state produced.

2. In no case did any local or general pathological process result from such inoculation.

3. In five instances influenza bacilli isolated later than 24 hours after inoculation were shown to be different strains from those introduced.

4. Influenza bacilli were viable after being suspended in saliva for 24 hours at 37° C.

5. The rapid disappearance of *B. influenzæ* from the upper air passages is probably due to the combination of an unfavorable environment with the mechanical flushing processes at work in those regions.

6. The question of the persistence of influenza bacilli in normal throats can not be finally settled until we possess accurate methods for differentiating various strains of hemophilic bacteria.

The question naturally arises as to what makes possible the tremendous growth of influenza bacilli in disease conditions such as sinusitis, pharyngitis, laryngitis, pneumonia, measles, "flu," etc. A possible explanation which

[81] Roos, C.: Notes on the bacteriology and on the selective action of *B. influenzæ* of Pfeiffer. Jour. of Immunology, 1919, Vol. IV.

[82] Bloomfield, A. L.: Fate of influenza bacilli introduced into upper air passages. Johns Hopkins University Bulletin, March, 1920, 349 : 85.

still lacks final proof is that these acute processes may alter the environment in such a way that the organisms take hold and grow rapidly at the seat of the disease.

Jordan and Reith [83] in their observations on the characteristics and occurrence of the hemophilic bacilli seem to find the influenza bacilli in the noses and throats of healthy individuals with almost the same regularity as in those of the sick. Their observations are so interesting that they will be given in detail:

Although as late as 1919 students of influenza felt able to say that "there is inadequate proof that the Pfeiffer bacillus is a member of the upper normal respiratory tract flora," subsequent observation indicated that typical Pfeiffer bacilli occur in perfectly normal persons, both as transient and as more or less permanent elements of the respiratory flora. Wolstein and Spence, however, express the opinion that an exceedingly small number of healthy persons carry the Pfeiffer bacilli in their respiratory tract "even during the time of an influenza epidemic," unless there is a history of direct exposure. Bloomfield, as the result of a comprehensive series of studies, concludes that the Pfeiffer bacilli have no more than a moderate and partial degree of adaptation to free growth on normal mucous membranes. There seemed, thus, reason for further examination of the normal throat flora to determine the presence, abundance, and seasonal prevalence of the Pfeiffer bacillus.

During the calendar year 1922, plates were made from the throats of 294 university students (about one-fifth being women) according to methods previously described, oleate medium being used throughout. With the first 120 examined, blood agar was also used, as already stated. At the time of examination, 271 of these persons were in apparently normal health, and the throat appeared to be in healthy condition. The Pfeiffer bacillus was found in 108, or 40 per cent, of the throats of these seemingly normal persons. In most instances in which positive findings were obtained, the number of Pfeiffer-like colonies on the plates was recorded as "several," "few," or "very few"; but in about 10 per cent there were "many" Pfeiffer-like colonies.

Information was obtained from 290 of 294 examined regarding influenzal history. The data secured were probably as accurate as could be obtained from any group. The results are as follows:

Influenzal history of persons examined for Pfeiffer bacilli.

History.	Number.	Pfeiffer bacilli found in—	
		Number.	Per cent.
No history of influenza	173	72	41
Influenza in 1918–19 epidemic	76	38	50
No influenza in 1918–19, but clinical influenza later [a]	41	23	56

[a] Sharply differentiated from an ordinary cold in the opinion of the person reporting.

[83] Jordan, E. O., and Reith, A. F.: Further observations on the characteristics and occurrence of the hemophilic bacilli. Jour. Inf. Dis., Mar., 1924.

Relation between colds and Pfeiffer bacilli.

History.	Number.	Pfeiffer bacilli found in—	
		Number.	Per cent.
Colds in progress at time throat was swabbed	64	37	58
Recent cold (within 1 month)	47	22	47
No cold within 1 month	95	39	41
No cold within 6 months	72	26	36
Chronic rhinitis	12	4	

One student reported never having colds, 2 had hay fever at the time of examination, 1 had been gassed and his throat was still affected; in none of them was the Pfeiffer bacillus found.

Pfeiffer bacilli found in normal and inflamed throats.

Condition of throat.	Number.	Pfeiffer bacilli found in—	
		Number.	Per cent.
Throat apparently normal at time of examination	271	108	40
Throat visibly inflamed at time of examination	22	12	54

R. H. Major,[84] of the University of Kansas, believes that the invasive power of the influenza bacilli is limited. He says:

1. When organisms are injected intravenously, the effects produced are to be explained by a toxic action rather than any direct bacterial action produced by multiplication through the blood streams. In no cases were *B. influenzæ* recovered from blood after injection.

2. Introduction of *B. influenzæ* into trachea was successful in producing broncho-pneumonia. Invasive powers were limited.

3. Preliminary initiation of respiratory tract with chlorine gas permitted extensive invasion with influenza bacilli injected intravenously and intratracheally.

COMPLEMENT FIXATION.

In furthering studies of the influenza bacillus, Katherine Howell and Ruth Anderson[85] did some work on complement fixation in influenza. They say:

The outstanding feature of this work on complement fixation with influenza serum is the large number of positive results with certain strains of the *viridans* group of streptococci isolated from cases of influenza at Camp Meade and in Chicago. The evidence indicates that such organisms probably played an important part in the morbid process even in other places. Serum from influenza patients in several different places appears to have acquired similar new properties.

[84] Major, R. H.: Experimental production of pneumonia with *B. pfeiffer*. Jour. of Med. Research, Boston, Mass., 1920, 41: 373.

[85] Howell, Katherine, and Anderson, Ruth: Complement fixation in influenza. Jour. of Inf. Dis., Vol. XXV, 1919.

AGGLUTINATION.

Jordan and Sharp [86] summarize the discussion of the agglutinating powers of the Pfeiffer bacillus as follows:

The serum of influenza patients agglutinates Pfeiffer bacilli to a greater degree and in a larger number of cases than does the serum of healthy persons. The same is true, however, of the serum of measles patients, so that the presence of agglutinins for the Pfeiffer bacilli in influenza serum can not be taken as evidence of any causal relation between this organism and influenza. There is no evidence that the observed increase in agglutinative power in measles serum is dependent in any degree on a secondary invasion by the Pfeiffer bacilli. The most plausible explanation seems to be that infections of various kinds increase the nonspecific or normal agglutinins of the blood, and that such relatively slight agglutination enhancement as is observed falls in this category and not in that of specific causal relation.

The Lancet (London) of February 16, 1924, comments on the work of Olitsky and Gates in the preparation of agglutinin serums for pneumosintes in the following manner:

The occurrence of a small wave of epidemic influenza in New York some months ago offered an opportunity for ascertaining whether the *B. pneumosintes* was concerned in this in the same way as in the 1918–19 pandemic, during which it was first isolated. In the course of their previous work Doctors Olitsky and Gates had been able to demonstrate that on injection of the organism into the blood stream of rabbits agglutinins were developed; they further showed that similar agglutinins appeared in the blood of human beings inoculated with suspensions of the dead organism. In their recent investigations they were able to demonstrate the presence of agglutinins active against the 1918–19 strain of *B. pneumosintes* in the blood of all patients examined. These agglutinins appeared as early as 10 days from the onset of the disease, and seemed to reach a maximum by about the seventeenth day. They persisted for some months—at least five—but not indefinitely, as was shown by the fact that the blood of persons who had suffered in the 1918–19 epidemic or 1919–20, but not since, was free from them. The agglutinin titer was low; even with special buffering of the antigen it seldom went beyond 1 in 40 in injected animals, and in the human cases a positive result at a dilution of 1 in 10 was taken as diagnostic. Antibodies were also demonstrable by a precipitin test. Granted that *B. pneumosintes* is confirmed as the etiological factor in the influenzal entity, these agglutinin and precipitin reactions may prove of great value.

Symptomatology.

As stated before, the great difficulty in establishing influenza definitely as a disease is the apparent failure to be able to give it a clinical entity. It is by no means clearly established symtomatically and there is no assurance that cases diagnosed as influenza during an epidemic year receive the same diagnosis when they occur sporadically and unassociated with other cases. In all probability, diagnoses

[86] Sharp, W. B., and Jordan, E. O.: Agglutinins for Pfeiffer bacillus in serum of influenza and measles patients. Jour. of Inf. Dis., March, 1924.

in the latter would be colds, coryza, bronchitis, and the like. In other words, symptomatically it is definitely linked with the common cold and, according to present standards, who can safely diagnose between a mild case of influenza and a bad case of common cold?

In this connection Dr. J. C. Regan [87] tabulated symptoms of 100 unselected patients with influenza at the Kingston Avenue Hospital, with the following results:

	Per cent.		Per cent.
Headache	100	Perspiration	23
Cough	100	Secretion of eyes	20
Backache	70	Pain in joints	14
Sore throat	64	Diarrhea	12
Chills	50	General soreness	12
Pain in limbs	34	Nosebleed	10
Vertigo	29	Pain in neck	7
Secretion of nose	28	Pain in abdomen	4
Vomiting	23		

W. T. Vaughan, in his epidemiological study of influenza, goes into the question of symptoms rather exhaustively, and I shall again quote him as being clear-cut and to the point:

> The manner of spread of epidemic influenza is constant in a primary epidemic, and the epidemic as a whole has certain features which render it characteristic. The sporadic case has, as a rule, the same clear-cut clinical symptomatology, but it fails to manifest the one feature most characteristic of epidemic influenza—a high degree of contagiousness. Further, although the symptoms in themselves are characteristic, there is no pathognomonic sign by which one may say, "This is a case of influenza"; and, finally, other disease conditions, such as tonsillitis, frequently resemble it so much as to cause error in diagnosis. * * * In the report of the chief medical officer of the Ministry of Health in the British Isles, George Newman, to the Minister of Health, Christopher Addison, on the pandemic influenza in 1918–19, certain pertinent remarks are recorded, as follows:
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> The influenza of the seventeenth century had as its most constant symptoms cough, vomiting, hemoptysis, aches, and weariness in the head, back, and limbs, and some fever. In addition, there was frequently thrush and epistaxis. According to Sydenham, the disease was of the nature of "epidemic ague" up to 1685, but afterwards changed its character to that of "pestilential fever." In 1729 Huxham, of Plymouth, described the disease as a "catarrhal febricula, racking pains in the head, delirium with incessant cough, slight dyspepsia, anorexia, languor, and rheumatic pains"; a few years later he characterized it as also having rigors, "flying pains" in the back, and violent headaches; and once more, after 10 years, he adds pains to the joints and universal lassitude as the leading features. In 1767 Heberden described the attack seen by him as beginning with severe chills, then a troublesome cough, acute pains in the head, back, and abdomen, with fever and prostration. Fifteen years later the College of Physicians said that "the universal and almost pathognomonic symptom was a distressing pain and sense of constriction in the forehead, temples, and sometimes in the whole face, accompanied with a sense of soreness about the cheek bones under the muscles,"

[87] Regan, J. C.: New York Medical Journal, Dec. 7, 1924.

with a languor of body and depression of mind. The influenza of 1833 assumed a catarrhal character—sudden attack, headache, coryza, and cough, pain in the chest, and depression; and in the great epidemic of 1847 these characters predominated, accompanied by pneumonia and bronchitis.

We have many contemporaneous accounts of the influenza of 1889–1892. The catarrhal symptoms receded into the background; extreme prostration, weakness, and nervous depression were the outstanding features. Frontal headache, pain in the eyeballs, and muscular pains were also common. In the later phases of that epidemic a tendency to lung complications was manifested, especially a "low and insidious form of pneumonia, to which the mortality from influenza was in large part due" (Parsons). Pye-Smith wrote a description in 1890 based on the first two years of the epidemic. He said that most of the symptoms were those of a "common feverish cold, attended with greater pyrexia and with more severe depression of strength." The attack began suddenly with rigors and pain "behind the eyes," prostration, pains in the limbs, and some faintness, and often an irritating dry cough. Sometimes there was great dyspnea and loss of appetite. The attack passed off at the end of three to five days. If it continued longer, pneumonia or bronchitis supervened. Convalescence was slow, with muscular weakness and malaise. The fatality was low. In the 25 years following 1890 influenza was widely prevalent in England and Wales—a condition totally different from its relatively quiescent stage between 1850 and 1889.

All observers are agreed as to the differentiating characteristics of the two waves, the first in June and July, 1918, the second in October and November, 1918 (the third, presenting the features of the second, in February, 1919). The first wave was one of the "three-day fever type." There was sudden onset, lassitude, and prostration, general aching, a rapid rise in temperature, a relatively slow but unstable pulse, coated tongue, loss of appetite, a sore throat, and a congested nasopharynx, headaches, a rapid convalescence, and a low mortality. Though the respiration was quickened, there was no dyspnea; gastrointestinal symptoms were common, but not severe; and, as a rule, there was no albuminuria. There were, of course, variations and complications, the most frequent involvement being the respiratory tract. Whilst coryza was rare, epistaxis and other hemorrhages were common; substernal pain occurred, and was worse owing to cough, which was almost universal. The progressive changes in the sputum were significant. The chief nervous conditions were psychical, and sleeplessness was common.

On its clinical side the outbreak was remarkable, not for its virulence or mortality, both of which were low, but for its complete change of age incidence. It attacked youth.

The clinical features of the second wave ushered in much more severe forms of the disease. As Docaor French points out, of a thousand individuals attacked in the autumn, about 800 suffered from the three-day-fever type, though of somewhat unusual severity. The remaining 200 displayed pulmonary complications; and of these 80 may be thought of as moderately severe, and 120 as desperately ill. Of the 120, between 60 and 80 would prove fatal (Abrahams). Many cases began as in the first wave, though epistaxis appeared to be particularly common. Some cases became pulmonary at the outset, others in a few hours or days. The pulmonary involvement was an acute infective inflammation, sometimes progressing as a broncho-pneumonia; at other times it swept through the body like a virulent toxemia or septicemia. In some cases there were few or no physical signs; in others dullness, bronchial breathing, crackling rales, bronchophony, and pectoriloquy;

In others signs of coagulative edema, hemorrhage, abscess, and collapse. The normal progress of a pneumonia case was rare. There was pain, headache behind the eyes, earache, cough, a high respiration rate (polypnea), variable fever, followed by a toxemic or pulmonary complication on the third or fourth day. The toxemia was heralded by early cyanosis, delirium, a rapid pulse, and epistaxis. The heliotrope cyanosis indicated a bad prognosis; and it was evidently not cardiac in origin, but an intoxication, recalling the purulent bronchitis experienced in 1916–17 at Aldershot (expectoration of enormous quantities of purulent sputum, heliotrope cyanosis, and high fatality), itself an infection due in part to *B. influenzæ* and in part to the *Micrococcus catarrhalis*, streptococcus, or associated organisms. There are grounds for believing that both forms of cyanosis were caused by an albuminous exudate in the alveoli and interstitial tissue of the lung. The pulmonary complications which arose were various, and included edema, broncho-pneumonia, hemorrhage, effusions, and sometimes abscess. The onset of the lung changes was indicated by alteration in the character of the sputum, increased respiration rate, pain, and diminished respiratory movements and air entry (Sundell). The mild type of the first wave and the contrasting type of the second and third waves seem to have been very much the same everywhere, except that different stages of the epidemic did not occur at quite the same periods or with uniform sequence in different countries.

Epidemic Cycles.

Since the earliest time when there was any knowledge of influenza or epidemic catarrh, it has been known that epidemics and pandemics develop with startling suddenness, run a comparatively short course, disappear, and periodically return. Although this phenomenon is known and future returns can be confidently expected, there is dispute as to the epidemic cycle.

John Brownlee,[88] of London, advocates the 33-week periodicity cycle, and in the Lancet says:

> Considering especially the years 1889 and 1896 as the most typical years, it is seen that the epidemics of influenza have had their maxima from the beginning of January to the end of May. Applying the ordinary method of the periodogram, it is found that the interval between epidemics is 33 weeks, there being a missed epidemic when an epidemic is due in the autumn. The periodicity is rigid within these years, though later years show considerable aberration. The method of the periodogram allows us to extend the knowledge acquired with regard to influenza to associated diseases, as bronchitis and pneumonia.
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> It is found, on examination, that between 1876 and 1890 there is no such periodicity with regard to bronchitis and pneumonia, but from 1889 to 1896 it is marked. Comparing the graphs for 33 weeks for the three diseases, influenza, bronchitis, and pneumonia, it is found that pneumonia deaths precede influenza deaths by a little over a week. The deaths from bronchitis have an epidemic rise 10 days before the rise of influenza. When several sets of deaths are added together in 33-week periods, a very typical epidemic makes its appearance.
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> What of the future? From July 13, 1918, to March 1, 1919, the maximum points of two of the last epidemics is 33 weeks. From March 1 to October 1

[88] Brownlee, John: The Lancet, Nov. 8, 1919.

is also 33 weeks. An epidemic is therefore due, but it falls at the unsuitable season of the year, and should, therefore, be small. With regard to the aberrant October epidemic, this might be expected to have been followed by an epidemic in June, the season of the year at which an epidemic is still possible but very unlikely. If the October epidemic, therefore, has a 33 weeks' sequence, the next epidemic of influenza would occur in January or February of the new year (1920).

As a matter of fact, Brownlee did, on this basis, prophesy the epidemic of 1920, which occurred in January of that year. Stallybrass,[89] of Liverpool, supports the observations of Brownlee in the following way:

I am able to supplement his investigations by the weekly deaths occurring in Liverpool during the period 1890–1918 that were ascribed to influenza and to all the respiratory diseases.

Stallybrass also calls attention to the epidemic years of England, which are 1789–90, 1802–3, 1830–32, 1840–41, 1848–49, 1854, 1869–70, 1879, 1890–91, 1898, and 1918. With the exception of 1854 all these dates are about the end of a decennium. The theories advanced by this author are as follows:

(1) Life cycle of the virus.
(2) Extrinsic changes.
(3) Changes in the host.
(4) Climate.

On the other hand, B. C. Spear,[90] of London, disagrees with Brownlee's periodicity of 33 weeks. More frequently Spear divides the year into 13 four-week periods, and his analysis of the weekly deaths in London show that influenza prevalence falls more frequently in the second and third four-week periods of the year. He says that this test shows that there is an approximation to a seasonal or annual period, and that the time mentioned by Brownlee in his forecast is in any year the most likely time for influenza prevalence.

In the American Journal of Hygiene,[91] W. T. Vaughan summarized his conclusions on the periodicity of influenza in this manner:

An influenza period usually comprises from three to five years, with one or two very mild epidemics at the beginning, which may be frequently overlooked, then of wide pandemic spread to be followed by endemic recurrences for as long as two or three years. During these influenza periods the intervals between waves are frequently so nearly equal or multiples of each other as to force the question of a periodic law. Not only this but even on a larger scale does the disease appear with a certain uniform regularity. The great epidemics are separated frequently by intervals approximating decades.

(1) Influenza does tend to recur at intervals. It has not been proved that these intervals are always of equal length.

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[89] Stallybrass, C. O.: The Lancet, Vol. CXCVIII, 1920, p. 372.
[90] Spear, B. C.: The Lancet, Mar. 13, 1920.
[91] Vaughn, W. T.: The epidemiology of influenza. Am. Jour. of Hyg., 1921, Monograph Series No. 1.

(2) At present, opinions concerning the periods are divergent. We have the 33-week periodicity of Brownlee and Stallybrass, the seven-week intervals suggested by Pearl, the one-year period of Spear, and the apparent 12-week recurrences in England in 1918 and 1919.

(3) Whether or not there is a regular periodicity of a definite number of weeks in the case of influenza, the fact remains that one of the dominant characteristics of epidemic influenza is its recurrence at intervals.

The only conclusion is that the question of the periodicity of influenza, like all other features connected with this disease, is as yet veiled in uncertainty.

Conclusion.

In this somewhat meager summary of the opinions of men who have given much time and thought to this baffling disease, it is obvious that there has been little advance in any definite knowledge concerning its etiology, epidemiology, periodicity, or the establishment of definite symptoms, pathognomonic in its diagnosis.

The close association of influenza with the minor respiratory diseases, especially that symptom complex which, for want of a better name, is called the " common cold," is suggestive of a possible clinical correlation between these two disorders (common cold and influenza) more intimate than has been recognized or conceded. There are cases of common cold and ordinary influenza which are almost indistinguishable clinically—in other words, a mild case of influenza and a bad cold overlap to such an extent that they may be designated by either diagnosis. The bacteriological findings in the noses and throats of influenza sufferers and those suffering from a common cold are the same; and even in health the bacterial flora found in the minor respiratory diseases are apparently ever present.

It can only be said at the present time that the status of the minor respiratory diseases, from the standpoint of medical nomenclature, is chaotic. The only remedy is to establish definitely, if possible, just what is a common cold and just what is influenza, at the same time discouraging the use of ambiguous terms such as " grippe " when referring to a bad cold, and " grippy condition " when speaking of a mild case of influenza. Either an ordinary common cold is a manifestation of another disease or it is a distinct and separate disease in itself. Much will be accomplishd when one or the other of these suppositions has been established.

As mentioned in the beginning of this article, the United States Public Health Service in 1923 undertook a study of the interepidemic occurrence and phases of influenza as well as other minor respiratory conditions. At the present time semimonthly reports are being received from 10,000 individuals in all sections of the United States as to whether or not they have suffered from any of

these disorders during the period in question. Reports are also being received from the families of officers in the Medical Corps of the Army and Navy and of those in the Public Health Service, together with the families of faculty members of eight universities, a total of 1,500 families.

It is anticipated that in the final analysis much information of value will be gleaned and that the occurrence of these minor respiratory conditions may be understood better, and also whether there is any relation between the minor respiratory diseases and the interepidemic phase of influenza. A study of symptoms and their analyses in correlation with the diagnoses presented is contemplated in the effort to arrive at a certain standardization.

This is the first time in the history of medicine that such a nationwide experiment in influenza research has been undertaken, and the results are awaited with interest in the hope that further light will be shed on a malady which is causing its deaths, its economic losses, and its distress, and about which we know so little.

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